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Elective uptake of radioiodine by cancer of the stomach

W. H. CLODE*
J. M. V. SOBRAL*
E. LIMA BASTO, F.A.C.S.
A. M. BAPTISTA*
LISBON, PORTUGAL
From the Laboratório de Isótopos Abílio Lopes do Rego, Instituto Português de Oncologia

It is well known that the stomach plays a part in the iodine cycle. The absorption of iodine through the gastrointestinal system happens very rapidly and the iodine concentration in the gastric juice reaches very high values as has been demonstrated with use of radioiodine as a tracer.[1]

Our attention was recently called to a patient who received a therapeutic dose of 16,000 rad of I^{131} for the treatment of very severe hyperthyroidism. Two months later the patient returned to our laboratory because of his awareness of a nodule in the lower left side of the neck.

A thyroid scan was performed which showed a definite uptake of radioiodine over the supraclavicular node. Histologic examination after biopsy showed a lymph node invaded by a neoplastic glandular structure which could be interpreted as a metastatic gastric carcinoma or, inasmuch as the histologic characteristics were not perfectly typical, as a possible thyroid neoplasm, the diagnosis being supported by the radioiodine uptake.

Six months later the patient died of cancer of the stomach which had been symptomatic for only 2 months, but had been too far advanced for surgical treatment. This case called our attention to the possibility that iodine could play an important part in the metabolism of gastric neoplasms and we now present our first results of this study.

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*Centro de Estudos de Física da Comissão de Estudos de Energia Nuclear do Instituto de Alta Cultura.

MATERIAL AND METHODS

In 6 cases in which cancer of the stomach was diagnosed by the usual clinical and radiologic methods, we administered intravenously 1 μc of I^{131} (carrier-free sodium iodine from the Radiochemical Center, Amersham) 24 hours before surgical intervention. The tumor was removed, carefully washed in normal salt solution, and fixed for 24 hours in formol. Fragments of the tumor and of normal stomach were taken

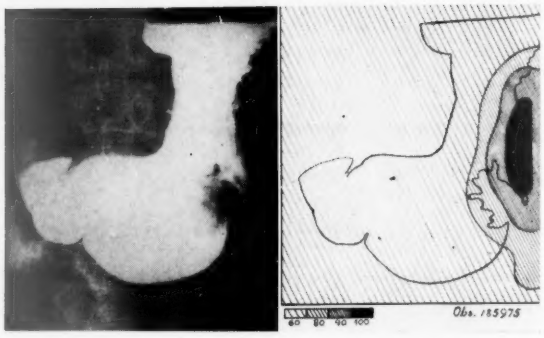

Fig. 1. Adenocarcinoma of stomach. Scanning of stomach after intravenous administration of 300 μc of I^{131}.

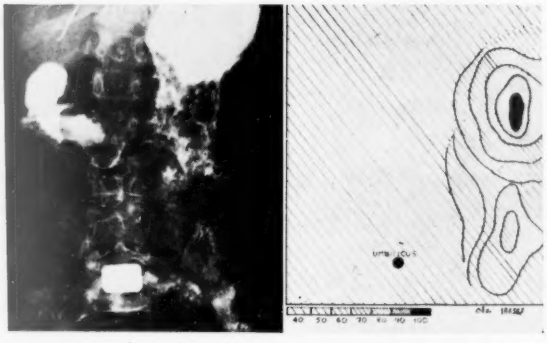

Fig. 2. Adenocarcinoma of stomach. Relatively increased radioactivity at the site of the cancer was shown by scanning after the administration of radioactive iodine.

and weighed and, after digestion for 24 hours in sulfuric acid, the radioactivity was measured in a well-type scintillation detector.

We studied only patients with the clinical diagnosis of cancer who were more than 50 years old, and therefore we were not particularly worried about the thyroid dose. Efforts are being directed toward making the use of much smaller amounts of radioiodine possible for the in vivo counting.

We believe from first results with a scanning apparatus which has a very much increased sensitivity and with photographic recording, that the I^{131} amount can be substantially reduced. In a few patients, radioactive scanning of the stomach was performed before the operation in order to discover if an increased radioactivity was to be observed over the tumor-bearing region.

For this purpose we used a manual scanner with a scintillation (thallium activated) sodium iodide crystal, 4 by 4 cm. shielded by 5 cm. of lead. The cylindrical aperture of the collimator had a diameter of 1.5 cm. and was 12 cm. high. The patient was in a dorsal decubitus position and the counter, perpendicular to the plane of the bed, was moved laterally to cover all the abdomen. Counting in each position was from 0.5 to 1 minute.

Table I shows the results obtained from specific radioactivity measurements of the normal mucosa and of the tumor tissues.

Fig. 1 shows the results of scanning over the stomach of Patient 2 after the intravenous administration of 300 μc of sodium iodine (I^{131}). The scanning showed a tumor of the greater curvature. This cancer was inoperable but a lymph node removed from the greater omentum during the operation had a higher specific radioactivity than the normal tissue. The results in a few other cases up to now always revealed the presence of tumors (Fig. 2).

One case was particularly interesting (Table I, Patient 6) in which the lesion macroscopically resembled an ulcerated carcinoma. As shown in Table I, the relation of tumor radioactivity to the normal radioactivity was less than 1. A careful histologic examination showed the lesion to be a callous peptic ulcer.

In order to disprove the suggestion that the higher concentration observed was due

Table I

Patient	*Tumor specific radioactivity* / *Normal tissue specific radioactivity*	*Observations*
1. E. T. B.	3.3	Adenocarcinoma
2. A. J. P.	3.4	Lymph node fragment with metastasis of inoperable adenocarcinoma
3. A. J. A.	3.5	Adenocarcinoma
4. P. P. V.	21.8	Adenocarcinoma
5. P. M.	30.9	Adenocarcinoma
6. M. R. C.	0.58	Callous peptic ulcer

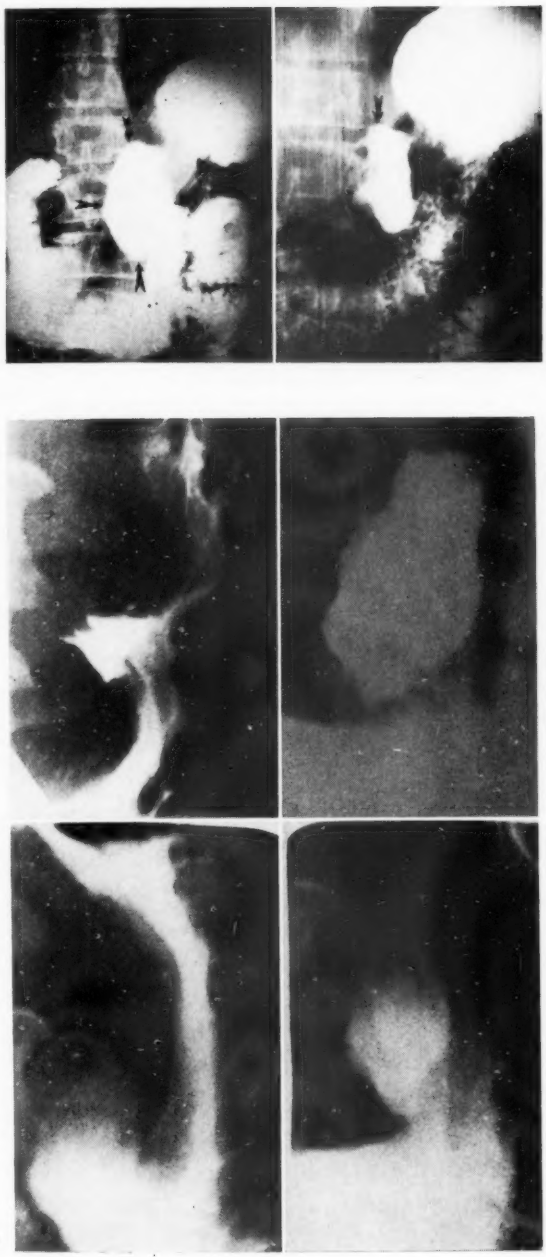

Fig. 3. *A,* Roentgenograms which offer a suspicion of cancer of the stomach. *B,* Scanning after the administration of radioactive iodine showed no specific concentration. Later gastrectomy showed the lesion to be a giant benign ulcer.

to an increased vascularization of the tumor without any specific concentration mechanism for iodine, a study was made in 1 case in which 300 μc of I^{131}-labeled human serum albumin was injected 15 minutes before the gastrectomy. We obtained for the relative radioactivity of tumor and normal tissue the value of 0.79.

It is also interesting to see that a suspected cancer of the stomach (Fig. 3) did not give the expected result after scanning. It later proved to be a giant benign ulcer. The scanning in other ulcer cases failed to show any specific radioactivity uptake.

SUMMARY AND CONCLUSIONS

In all of the patients studied until now, it was shown that cancer of the stomach is indeed able to pick up radioiodine and that its specific radioactivity is higher than that of the normal gastric mucosa.

Scanning over the stomach region also showed a higher concentration of the radioactivity over the tumor in accordance with the previous findings. These facts suggest a new diagnostic procedure for cancer of the stomach, because in normal patients (hyperthyroid patients who were treated with radioiodine) we have never observed similar findings.

The results are particularly interesting because until now, an increased radioiodine uptake detected over a region was related to the possible existence of a metastasis of thyroid cancer.

Work is being done to extend the number of observations and, in particular, to study the biochemical and metabolic aspects of this problem and its possible implications in the diagnosis and therapy of cancer of stomach.

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A simple cooling device for treatment of upper gastrointestinal bleeding

MARSH H. HOLT, M.D.
CHICAGO, ILL.
From the Department of Surgery, Northwestern University Medical School

The use of local hypothermia in the treatment of upper gastrointestinal hemorrhage as recently introduced by Wangensteen[3-5] and his associates has gained increasing interest and trial. The rationale behind this technique stems from the studies by Wangensteen which demonstrated the effectiveness of local hypothermia in depressing peptic activity, suppressing gastric secretions, decreasing bowel motility, and diminishing local blood flow.

The routine practical use of local hypothermia for intractable hemorrhage, however, is limited to centers with the specialized equipment and personnel necessary for this type of procedure.

Utilizing our experience derived from the use of intragastric cooling in general hypothermia,[1, 2] we have developed a simple, safe, and inexpensive device which can be used in a routine hospital procedure in the treatment of uncontrolled upper gastrointestinal hemorrhage.

MATERIALS

The device consists of a basic pump–cooling unit (Fig. 1, *A*), plastic tubing with intragastric or esophageal balloons (Fig. 1, *B* and *C*), and a physiologic cooling solution. The unit can be used with either an open or closed circulation system.

The pump–cooling unit is composed of (1) a heat exchanger, (2) a fluid reservoir, (3) an automatic leveling device, and (4) a small centrifugal pump.

The heat exchanger is composed of 18 feet of three-eighths inch Tygon plastic tubing wound in a spiral fashion around a stainless steel frame. The unit is constructed to fit within a common operating room bucket and to be covered with chipped ice. A monitoring thermometer is interposed at the inflow and outflow ends of the tubing.

The fluid reservoir is a 1 L. graduated Lucite cylinder which is attached to the steel framework above the ice level. It is used only during open-circuit perfusion. The cooling solution drains by syphon from the stomach and enters the top of the reservoir through a screen filter. The fluid is then drawn from the reservoir via a bottom outlet and pumped through the heat exchange unit and back into the stomach.

The automatic leveling device, used only with the open-circuit technique, is attached to the reservoir where it serves to maintain a constant circulating volume. The device employs an Acro snap action switch* which is mounted on the reservoir and attached by a lever to the end of a finger cot connected directly to a nipple on the reservoir. As the reservoir fluid level varies with the outflow-inflow difference, the finger cot fills or collapses, moving the attached switch lever causing an on-off regulation of the pump. The sensitivity is adjustable to within 50 ml. by alteration of the position of the switch. During closed-system use the leveling device is bypassed and constant circulation is maintained. A 3-way master switch provides an on-off or automatic setting.

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*Acro Switch Company, Columbus, Ohio.

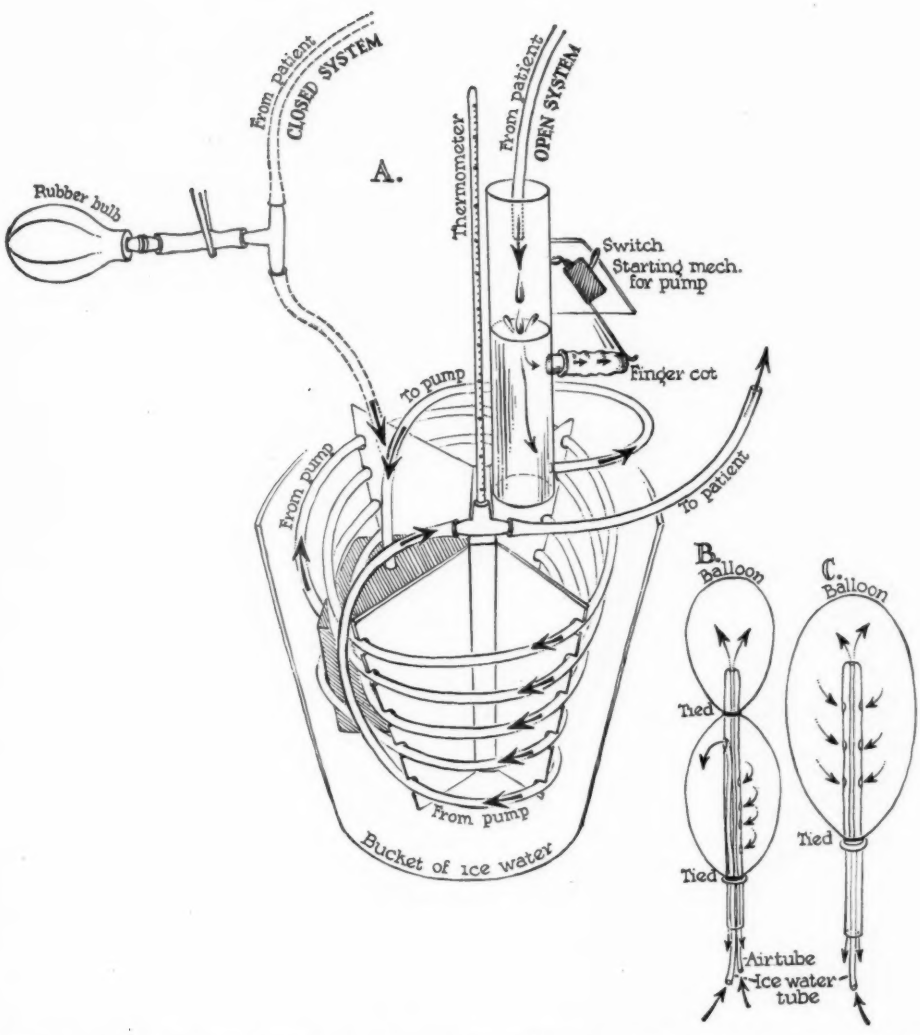

Fig. 1. *A,* Schematic drawing of the cooling unit assembled and in use which shows both open system (solid-line tube from patient) and closed system (broken-line tube from patient). *B,* Balloon used for cooling and compressing bleeding esophageal varices. *C,* Balloon used for closed-system cooling of the stomach.

The pump used is a small, submersible centrifugal sump pump ($25.00) with a removable brass head (Little Giant*). The pump is attached to the steel frame and submerged in ice to maintain a safe operating temperature.

The tubing with intragastric and esophageal balloons is shown in Fig. 1, *B* and *C*. This can be easily made from an 18 Fr. K-55 Pharmaseal urinary drainage tube as an outer shell and an inner tube of polyethylene (PE320). A condom is attached to the outer shell with thread to form a sealed circulation chamber. The esophageal unit contains a small additional tube leading to a separate intragastric compartment which can be filled with air or water. The appropriate intraesophageal pressure, according to the Sengstaken principle, is determined with a single mercury manometer connected to the closed circulation system.

During open circulation, a Levin tube for inflow is placed in the stomach via one nostril, while an 18 Fr. K-55 Pharmaseal multiperforated outflow tube also lies within the stomach after being passed through the other nostril.

The fluid used for open intragastric perfusion is that recommended by Wangensteen

*Little Giant Vaporizer Company, Oklahoma City, Okla.

Table I. *Open-system cooling solution*

Glucose	50 Gm.
NH_4Cl	2 Gm.
KCl	0.75 Gm.
$NaHCO_3$	add to adjust pH to 7.4
Distilled water	1 L.

From Wangensteen.[3]

(Table I). We have used this solution on 4 occasions in the induction of general hypothermia and have perfused the stomach for 4 hours in each instance. Evaluations of pH and potassium, sodium, and chloride levels in the solution before and after perfusion showed only an average decrease in pH from 7.4 to 5.2 and no significant electrolyte alterations.

METHOD OF OPERATION

The patient is examined to determine the site of hemorrhage as nearly as possible (esophageal varices or gastric or duodenal lesion). An attempt is then made to relieve the stomach of clotted blood by an orally inserted Ewald or colon tube.

After passage of a nasogastric Levin tube, the appropriate cooling tube is inserted by way of the other nostril. Cooling in the closed system is started after distention of the balloon with 300 ml. of water by way of a T connector or in the open system after filling of the stomach with the same amount of cooling solution.

During closed-system perfusion, constant gastric lavage with cold saline solution is performed through the Levin tube until there is no evidence of further hemorrhage. Constant low suction is maintained thereafter.

During open perfusion, the stomach is evacuated every hour and the fluid lost through the pyloric canal replaced. The average loss was 100 ml. per hour.

When the fluid is circulated at 600 ml. per minute, the temperature of the cooling fluid is from 5 to 10° C. and that of the returning fluid is approximately 4° C. higher in the closed system and 7° higher in the open system.

The total fluid contents of the cooling apparatus is 1,200 ml. in the open system. The stomach contains 300 ml., the heat exchanger 400 ml., and the reservoir approximately 500 ml. In the event that the automatic leveling device should fail, only the contents of the reservoir could be pumped into the stomach. This protection against acute severe gastric distention is possible because of the limited capacity of the unit and the inherent inability of the pump to function when filled with air from the empty reservoir. The closed system contains 700 ml. of water, 300 ml. of which is in the stomach balloon.

SUMMARY

An inexpensive, relatively simple, and safe apparatus is described which can be used by the average house officer in the primary treatment of uncontrolled upper gastrointestinal hemorrhage.

This device, in a modified form, will be available shortly from Gorman-Rupp Industries, Inc., Bellville, Ohio.

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Treatment of cardiospasm (achalasia of the esophagus) in children

W. SPENCER PAYNE, M.D.
F. HENRY ELLIS, JR., M.D.
ARTHUR M. OLSEN, M.D.
ROCHESTER, MINN.
From the Mayo Clinic and Mayo Foundation

Cardiospasm, or achalasia of the esophagus, although commonly encountered in adults, is rare in children. Moersch[6] found 12 patients less than 14 years of age in a series of 691 patients treated for cardiospasm. Among adult patients in that series, less than 5 per cent had the onset of symptoms during childhood. Olsen and associates[8] noted a similar incidence in their series of 601 patients. Only a few reports concern this condition in children, and more information is needed with regard to the methods of management and results of treatment in this age group.

MATERIAL

The present study is a review of the cases of 27 children 14 years of age and younger who were treated for cardiosapsm at the Mayo Clinic in the 25-year period from Jan. 1, 1935, through Dec. 31, 1959.

The diagnosis of cardiospasm was established in each case on the basis of characteristic symptoms and roentgenographic findings. Eight patients underwent esophagoscopic examination, in addition to the usual diagnostic studies, as part of the diagnostic investigation. Because of technical difficulties in performing esophageal motility studies in the very young,[7] complete documentation of the diagnosis of cardiospasm by this method was available in only 4 cases.

Eleven of the children were female and 16 were male. The 27 patients ranged in age from 13 months to 14 years (Table I) when first seen. The duration of symptoms ranged from 1 month to 10 years and averaged 2.6 years. The apparent age at onset of achalasia according to duration of symptoms is shown in Table II.

Regurgitation and obstruction to swallowing were the most frequent complaints, and weight loss or failure of growth and development were the second most common. Occasionally, weight loss of 30 to 40 pounds was encountered in children with severe obstructive symptoms. Less than half complained of pain referable to the esophagus. Nine had experienced recurrent episodes of pneumonitis secondary to aspiration of esophageal contents.[1] Children with cardiospasm were more severely incapacitated by their symptoms than were adult patients. However, the severity of the disease with respect to the degree of esophageal dilatation noted on initial roentgenograms of the esophagus was less in these children than we have noted in adult patients.[8, 9] In the present series, only 6 patients had severe dilatation. The rest had either mild or moderate dilatation.

Eleven of the patients had undergone some form of esophageal dilation, usually on multiple occasions, prior to examination and treatment at the clinic. It was either the recurrence of symptoms after treatment or the failure of previous dilations to relieve symptoms that caused these patients to seek additional medical aid.

METHODS OF TREATMENT

Since there is no known means of restoring normal peristaltic activity to the esoph-

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Table I. *Age distribution of 27 children with achalasia of esophagus*

Age (yr.)	1	2	3	4	5	6	7	8	9	10	11	12	13	14
No. of patients	1	4	1	–	–	4	–	2	3	–	2	2	4	4

Table II. *Apparent age at onset of achalasia in 27 children*

Age (yr.)	0-¼	½-1	2	3	4	5	6	7	8	9	10	11	12	13	14
No. of patients	5	5	–	–	1	2	2	2	–	2	2	1	4	1	–

agus in patients with achalasia, treatment at present is limited to relief of the distal esophageal obstruction. In the present series this was accomplished either by mechanical dilation of the cardia or by esophagomyotomy.

The preferred method of esophageal dilation for cardiospasm at this institution is hydrostatic dilation by means of a Plummer hydrostatic dilator,[8] which is passed over a previously swallowed thread. However, in some small children and in infants hydrostatic dilation may be hazardous, and some of these patients were treated by the passage of graduated sounds or bougies only. In children, unlike in adults, general anesthesia is occasionally required for these procedures.

Surgical treatment was undertaken in some patients who had failed to respond to mechanical dilations. Esophagomyotomy by means of a modified Heller procedure[2, 9] was the only surgical treatment employed in this series.

Thus, of the 27 children in this study, 26 were treated by dilation (8 by bougienage only and 18 by hydrostatic dilation) and 5 patients were treated by esophagomyotomy, 4 of them after previous treatment by mechanical dilations. One patient had only surgical treatment.

RESULTS OF TREATMENT

For the purpose of evaluating the results of treatment, the entire group was divided into patients who had received conservative treatment (mechanical dilation, 26 cases) and those who received surgical treatment (esophagomyotomy, 5 cases). Thus, 4 patients are included in both groups, namely, those who first received conservative treatment and, that failing, then underwent operation.

No hospital morbidity or deaths occurred in the group treated conservatively. All patients experienced symptomatic improvement immediately after the first course of treatment.

Among the 5 patients who underwent surgical treatment, all noted immediate and gratifying relief of their symptoms after operation. Only 1 patient experienced significant postoperative complications; empyema developed, necessitating decortication of the lung. No hospital deaths occurred among the group operated upon.

Late results. Complete follow-up information in the form of clinic examination or response to follow-up letters or both was available for review for 25 of the 26 children treated by dilation and for all 5 of those treated surgically.

Among the 25 children treated by dilation, the length of follow-up ranged from 1 to 19 years and averaged 9.6 years. The length of follow-up in the surgical group ranged from 1½ to 3 years and averaged 2.3 years.

The criteria for evaluating the effectiveness of treatment were similar to those used in previous studies.[2, 8, 9] The over-all effectiveness of treatment was judged with regard to the need for additional treatment and the status of the patient at the time of the most recent follow-up contact. Thus, the patient's condition was judged as being "improved" only if lasting symptomatic remission followed the initial trial of a given form of treatment. It was considered "poor" if additional treatment of the same or of a different type was necessary to relieve the patient of his symptoms.

Patients were classified as having excellent

results if they were completely asymptomatic, had gained weight, and had returned to full activity. They were classified as having good results if they fulfilled the aforementioned requirements but continued to notice occasional dysphagia when eating too rapidly or when nervous. Certain types of food, such as apples, raw vegetables, or peanut butter, may occasionally inconvenience these patients. Patients were judged to have fair results if they fulfilled most of the basic criteria and were definitely improved but continued to have occasional to frequent episodes of dysphagia with certain foods and occasional regurgitation. Patients were classified as having poor results if they showed no improvement or had a worsening of the condition.

The results of late follow-up of patients treated by conservative means were generally unsatisfactory (Table III). Of the 8 patients treated by simple bougienage, 3 have had persistent improvement and 5 had recurrence of symptoms within 1 year of the initial treatment. In the 3 patients who showed improvement, the results were only fair at the time of follow-up. All 5 patients who experienced recurrence of symptoms have been retreated by other means.

Of the 17 patients treated by hydrostatic dilations, 7 have had persistent improvement since the first treatment (Table III). Ten patients had recurrence of symptoms and required retreatment. Symptoms recurred in this group from 6 months to 4 years after initial treatment. The status of the 17 patients at the time of the last follow-up contact, including the results of all retreatments, was excellent in 2, good in 3, fair in 5, and poor in 7. Unfortunately, the data are incomplete with regard to the number of retreatments that were necessary to accomplish these results; many of these children have undergone subsequent dilations elsewhere. However, some are known to have improved with as few as 2 courses of treatment and others with as many as 12 at our institution. No morbidity or deaths were associated with any of the retreatments in this series.

The late results of surgical treatment have been most gratifying (Table III). All 5 patients have had persistent improvement. Four had excellent results and 1 good. None of these patients has required retreatment of any type, and none has experienced esophageal reflux or other late complications. The data in these 5 cases are considered in detail in Table IV.

COMMENT

The present study seems to confirm previous reports that the late results of mechanical dilation of the esophagus for cardiospasm are less satisfactory in children than they are in adults.[8] On the other hand, esophagomyotomy by means of a modified Heller procedure seems to offer the best means of producing sustained symptomatic improvement in patients of all ages.[9]

The children in this study who were treated by mechanical esophageal dilation have required many courses of treatment,

Table III. *Late results of treatment of 26 children with achalasia*

Type of treatment	*No. of patients**	*Results of treatment*				*Average duration of follow-up (yr.)*
		Improved			*Same or worse*	
		Excellent	*Good*	*Fair*	*Poor*	
Conservative						
Simple bougieneage	8	0	0	3	5	7.3
Hydrostatic dilations	17†	1	1	5	10	11.2
Surgical						
Modified Heller procedure	5	4	1	0	0	2.3

*Four of the patients included in the surgical group received conservative treatment initially and are listed also in that group.

†One patient treated by hydrostatic dilation was lost to follow-up and is not included.

Table IV. *Late results of Heller operation for achalasia in children**

Case No.	*Age (yr.)*	*Sex*	*Duration of symptoms (yr.)*	*Duration of follow-up (yr.)*	*Result*
1	3	F	1	3	Excellent
2	14	F	1	2½	Excellent
3	6	M	5	2½	Excellent
4	9½	M	1½	2	Excellent
5	11½	M	1	1½	Good

*All patients except 1 (case 3) had undergone previous treatment. Moderate dilatation of the esophagus was present in all 5 patients.

often over a period of years. Some have had to continue such treatment into adult life. Treatment by bougienage alone has rarely given more than temporary relief. Hydrostatic dilation, if it is to be effective, must be a drastic procedure, and often the endoscopist performing the dilations is unwilling to be as vigorous in these small patients as he might be in the adult. The necessity for general anesthesia in some of the very young patients undoubtedly increases the risk of the procedure.

In spite of the many unfavorable aspects, esophageal dilation was accomplished with little risk to the patient in this series. This procedure is capable of producing good symptomatic improvement for short periods and can be used in lieu of gastrostomy in preparing the severely malnourished child for more definitive treatment. Hydrostatic dilations seem preferable to simple bougienage, and an occasional patient may sustain a satisfactory remission of several years' duration. Unfortunately, the larger the number of dilations required, the less favorable the result. Local reaction produced by repeated dilations could lessen the surgeon's chance of obtaining a completely satisfactory result.

Experience with the surgical treatment of achalasia in infants and children has been limited. King[5] reported good results with esophagomyotomy in a 6½-month-old infant. Ferguson and Burford[3] operated on several children, the youngest of which was 9 months of age. Others have reported their experiences with the Wendel[10] and the Grøndahl[4] procedures in children with achalasia.

Esophagomyotomy by means of a modified Heller procedure is the preferable surgical treatment for cardiospasm. In the patient with symptoms whose general condition permits, we see no reason to delay operation because of age once the diagnosis has been established. Some form of definitive therapy is desirable before the esophagus has become greatly distended and decompensated. Thus, it appears that the younger the child, the greater the indication for surgical treatment as opposed to mechanical dilation. The growth factor does not appear to have any particular effect on the end result in these young patients treated by myotomy.

The diagnosis of cardiospasm may be difficult to establish in infants and children. They are often unable to cooperate satisfactorily for the necessary diagnostic studies, particularly for studies of esophageal motility. Occasionally, surgical exploration will be indicated to rule out some other condition. Malignancy in this region is rare in children. However, 2 patients not included in this study underwent surgical exploration after a clinical diagnosis of cardiospasm and were found at operation to have lower esophageal leiomyomas, which accounted for their symptoms. Satisfactory esophageal motility studies could not be obtained in these cases because neither patient was old enough to make this possible. The need for techniques of performing such studies in infants and children is obvious.

SUMMARY

Cardiospasm, or achalasia of the esophagus, is rare during infancy and childhood, but it should be considered in the differential diagnosis of young patients with feeding problems, regurgitation, and dysphagia. There is nothing characteristic about the patient's age at onset of symptoms. The

degree of esophageal dilatation is often less than that seen in adults with this condition, although the symptoms are usually more severe. Often the diagnosis is difficult to establish in this age group.

Several forms of treatment were employed in the present series. Of 5 patients treated surgically by means of a modified Heller procedure, the results were excellent in 4 and good in 1. Patients treated by repeated hydrostatic dilations or by simple bougienage had comparatively poorer results.

It is concluded that the modified Heller procedure can be used effectively in the treatment of infants and children with achalasia; it is the treatment of choice when the diagnosis is established in the patient with symptoms. Dilation therapy can be used effectively in lieu of gastrostomy in preparing the severely malnourished patient for operation.

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The 2-limb temporary gastrostomy tube

MARIO E. JASCALEVICH, M.D.
NEW YORK, N. Y.
From the Surgical Department, New York Polyclinic, Medical School, and Hospital

A review of the literature of the past 50 years shows several reports on the role of nasogastric intubation in the development of lesions of the upper respiratory and digestive tracts, and particularly in the production of ulcerative and later stenosing esophagitis.[2, 4-10] Because of this experience there is an increasing tendency in surgical centers across the country to resort more often to temporary gastrostomy in aged, debilitated, and poor-risk patients who will not tolerate a nasogastric tube well. Temporary gastrostomy would also be indicated in situations in which there is a history of nasopharyngolaryngeal or esophageal disease. Highly emotional and uncooperative individuals are also candidates for this procedure. In all such cases a lower incidence of pulmonary complication, a more comfortable patient, and the guarantee of a suction system that is very effective and easy to maintain are early rewards of temporary gastrostomy. Moreover, operations on the upper gastrointestinal tract in those situations can be further assisted if, in addition to the advantages of direct gastric drainage which avoids the nasal route, there could be independent suction from the stomach and/or afferent anastomotic loop and injection of feeding solutions into the efferent loop. The pioneering work of Abbott and Rawson[1] and others[9] partially accomplished this plan. Their device is a nasogastric tube with a single body and double lumen which, when used after gastroenterostomy and Billroth II gastrectomy, does not allow for suction in situ of the afferent loop that is particularly prone to obstruction and should be better kept decompressed. Mersheimer[12] in 1942 made the first attempt to do this by using dual and separate tubes for suction and feeding. He employed 2 No. 12 Levin tubes coupled with silk ligatures which were passed through the nose down to the stomach prior to operation. At this time, before performing the anterior layer of the gastroenterostomy, the surgeon places the distal ends of these tubes separately in the corresponding anastomotic limbs of the jejunum. Although in our hands the system appeared to be poorly tolerated by the patient and shares the criticism of nasogastric intubation in general when applied in the particular situations discussed, its principle stands with regard to the importance of direct and independent care of the proximal and distal anastomotic loops. This was accomplished successfully with our 2-limb temporary gastrostomy tube, an appliance which allows for jejunal feeding together with suction of the afferent loop, while at the same time provides the advantages of a gastrostomy type of drainage. As intravenous alimentation becomes replaced by enteral feeding, this device will render a particular service in postoperative recovery after upper gastrointestinal operations on patients with cardiorespiratory decompensation who otherwise would stand the double burden of an intravenous drip and the partial upper respiratory obstruction produced by the nasogastric tube. Moreover, in radical operations for carcinoma of the same area the device offers

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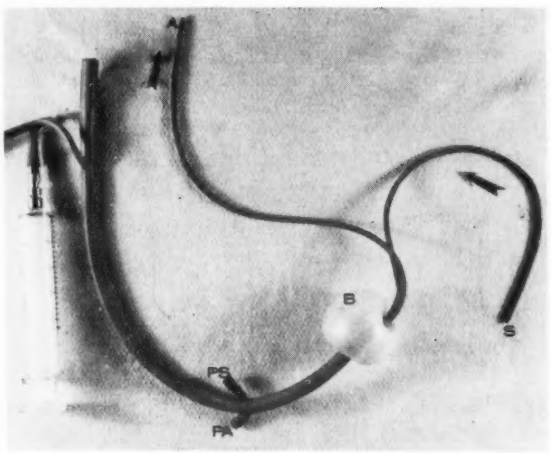

Fig. 1. Two-limb temporary gastrostomy tube with balloon inflated. *B,* Balloon; *A,* alimentary limb; *PA,* proximal end of limb *A*; *S,* suction limb; and *PS,* proximal end of limb *S*.

a solution to the double need for effective suction and the early administration of a complete nutritional support.

DESCRIPTION OF THE INSTRUMENT

The 2-limb temporary gastrostomy tube (Fig. 1) has been improvised very effectively. The tip of a No. 28 Foley catheter is cut off just distal to the bag *(B)* and through its lumen the proximal ends of 2 No. 12 Fr. red tubes are passed *(S)* and *(A)* which emerge at a variable distance from the balloon, approximately 10 to 12 cm. *(P.S.* and *P.A)*. For this purpose, 2 parallel orifices are made on the shaft of the Foley catheter at that level, with care not to enter

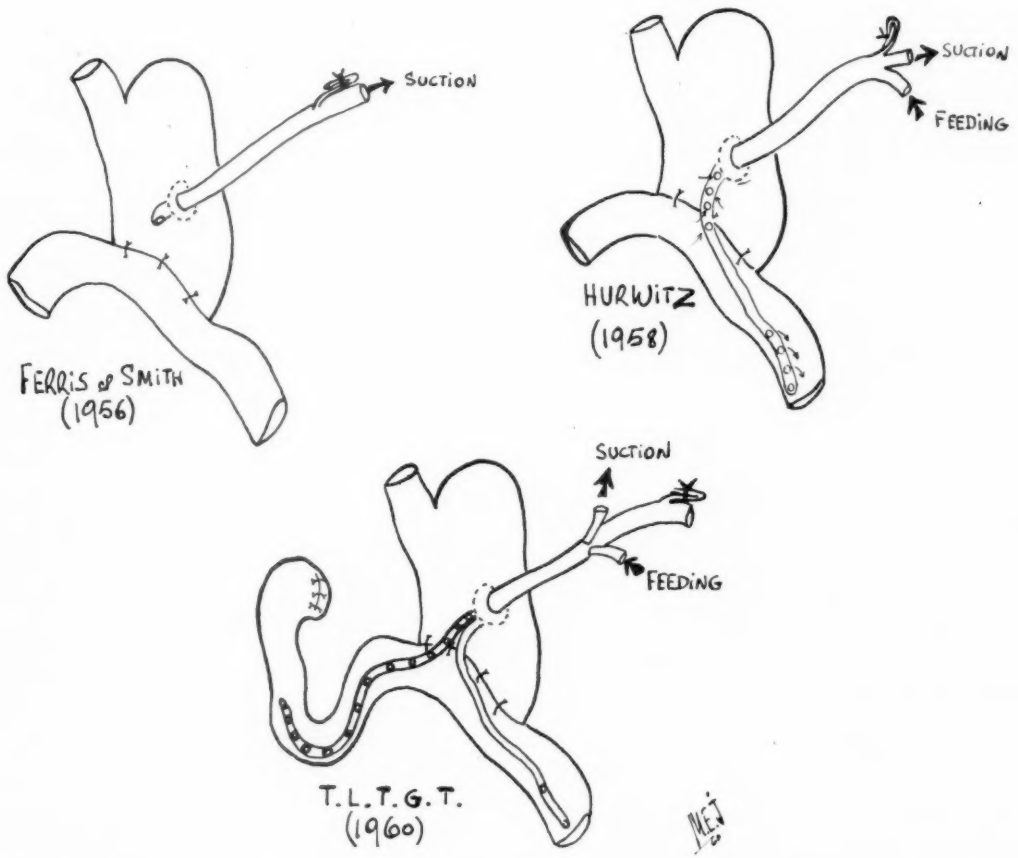

Fig. 2. The temporary gastrostomy tube described compared with other previously described models.

the channel that governs bag inflation. The openings permit snug passage of each French tube. These emerge from the host catheter for a distance of 2 cm. which is enough to insure connecting ends for the feeding and suction lines without undue shortening of the limbs of the instrument. Thus, the legs will measure 12 to 13 cm. long and can be prepared as necessary for their future use. The aspirating limb *(S)* will have multiple orifices cut out along the entire length at intervals of 2 cm. which are of a diameter sufficient to allow good suction without weakening the shaft of the tube itself. The feeding limb *(A)* will have only 1 orifice made at the distal end, about 2 cm. from the tip. To insure easy identification, the body and the cuff of each red tube are properly marked "suction" or "output" and "feeding" or "input." This will prevent cross misplacement of the aspirating and alimentary lines by the surgeon and misconnections by the staff in charge of the postoperatory care. When the integrity of the balloon and the patency of the channels have been tested, the 2-limb temporary gastrostomy tube is ready for use. Fig. 2 shows the type of gastrostomy tube used by Farris and Smith[6] and the model of Hurwitz[9] in comparison with the one described.

CLINICAL APPLICATION

A gastrotomy by the usual technique for gastrostomy is performed and each limb of the tube is introduced (with the help of a director if preferred) and placed. The aspirating limb is passed to the segment where suction is needed, either the stomach, duodenum, or afferent loop of a gastroenterostomy (Fig. 3), and the feeding limb is introduced far along the duodenum or efferent loop, depending on the particular situation. The distal end of the Foley catheter is then passed inside the stomach, the

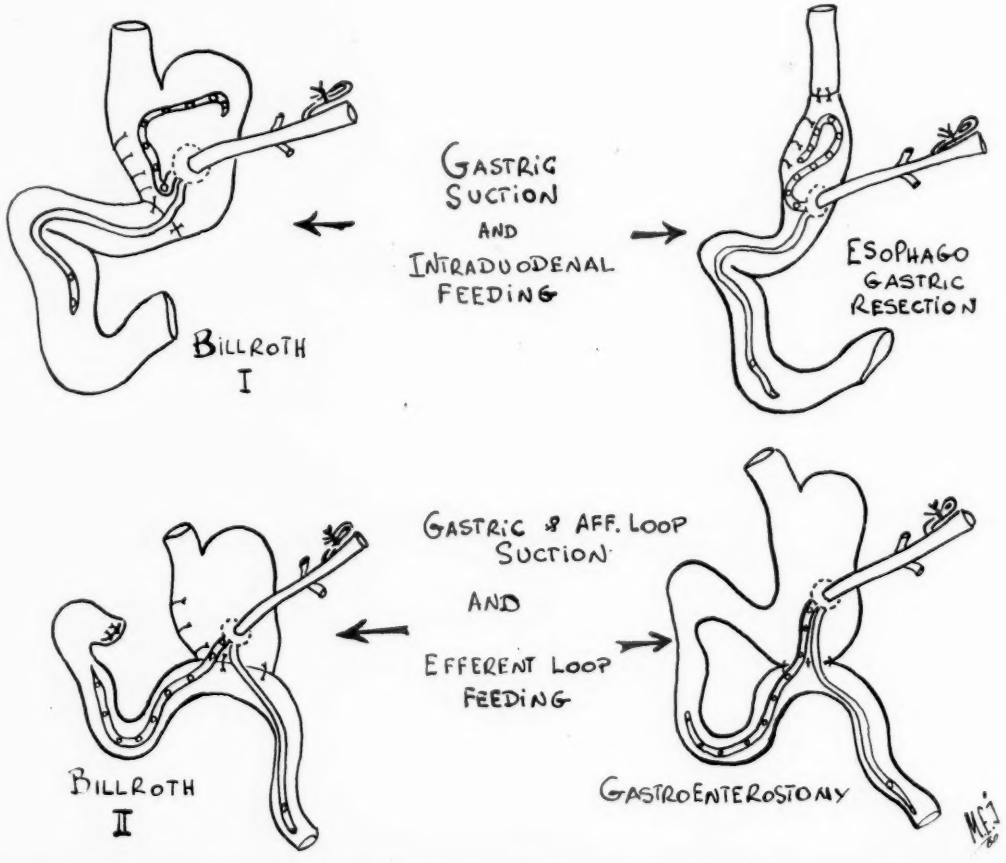

Fig. 3. Different situations in which the 2-limb tube can be applied advantageously.

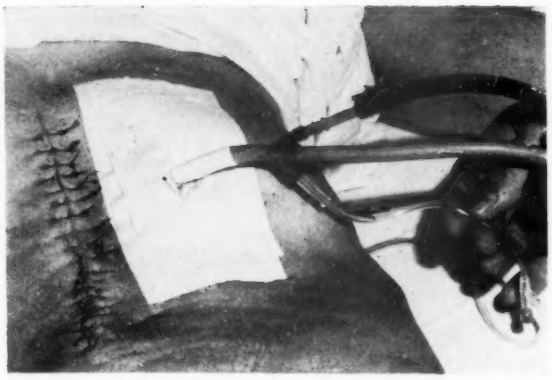

Fig. 4. Actual patient with tube applied. Note input and output lines *(arrows)* approaching the body of the Foley catheter through which they will reach the gastric lumen.

balloon inflated, and the gastrostomy completed with a typical Stamm technique. The proximal end with the twin French tubes is brought out of the abdomen through a stab wound. Finally, a silk stitch is placed to fix the Foley catheter to the skin edge of the stab incision.

Immediately after operation the output end of the tube is connected to a Wangensteen intermittent suction machine and the desired drip solution is attached to the input end. Twenty-four to 48 hours after the procedure a highly blended liquid feeding mixture can be passed through the input line. The aspirated fluids, if aseptically collected, could also be injected through this channel when necessary. Fig. 4 shows a typical 2-limb temporary gastrostomy tube in use.

SUMMARY

A 2-limb tube for temporary gastrostomy which permits simultaneous and independent suction and jejunal feeding is presented and its mode of use described. Its particular value in gastroenterostomy and Billroth II gastrectomy is stressed, as well as its application after upper gastrointestinal operations on patients with cardiorespiratory decompensation and radical resections for carcinoma in the aged and debilitated individual.

Our recent favorable experience with emergency gastrostomy and insertion of a 2-limb tube in a case of severe duodenal fistula after a Billroth II gastrectomy, which allowed an effective aggressive approach of the blow-out of the stump, will be the subject of a future report.

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Magnetic intubation

H. FRANK McCARTHY, M.D.
H. PHILIP HOVNANIAN, M.S.
TIMOTHY A. BRENNAN
PHILIP L. GAGNER, B.S.
WILMINGTON, MASS.
From the Research and Advanced Development Division, Avco Corporation

External magnetic forces may be used to guide a gastroduodenal tube through the pylorus into the duodenum. The system has provided successful decompression in patients with obstruction in a few minutes. This technique eliminates the delay associated with usual intubation methods and permits more rapid intestinal decompression in patients with serious distention.

A small permanent magnet is imbedded within the tip of a Cantor or Miller-Abbot tube. This tube is introduced into the stomach in the usual manner. It is then externally directed through the pylorus with the aid of the electromagnet.

THE ELECTROMAGNET

Six different electromagnets were fabricated and tested for magnetic field intensity, heat generation, weight, and power requirements.

Figs. 1 and 2 demonstrate the final design of electromagnet in position on the right flank of the subject. A central iron core is wound with aluminum strips (instead of copper wire) in order to reduce weight to approximately 14 pounds. A thumb microswitch on the magnet handle turns the power on or off. The magnetic field configuration has been designed to diminish excessive attraction of the tube as it approaches the magnet face. This provides a gentle pull upon the tube tip at all times, regardless of the relative proximity of the magnets. The thumb-controlled microswitch provides intermittent attraction at will and minimizes magnet heating. The direct current power supply of the electromagnet operates from an alternating current line at

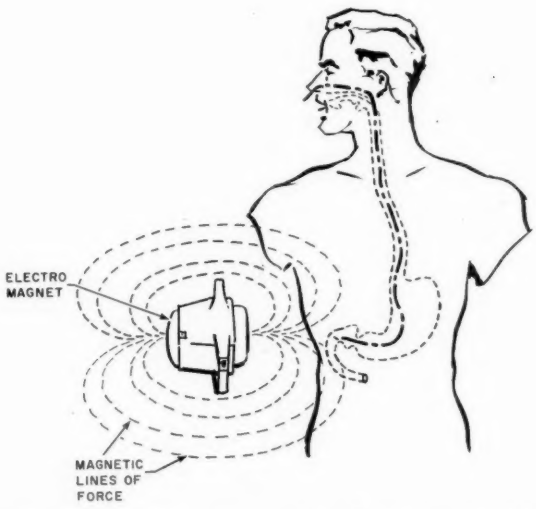

Fig. 1. Magnetic intubation diagram shows relative position of external magnet for transport through pyloric sphincter. Note that body does not present any insulation to magnetic lines.

Fig. 2. Schematic photograph shows the relative positions of external electromagnet and the gastroduodenal tube with embedded magnet.

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115 v. and a little under 15 amp. at maximum power.

At times some manipulative procedures are concurrently needed, for example, freeing of the tip of the gastroduodenal tube from a stomachic fold caused by intestinal distention.

CONCLUSION

Tests on patients indicate that the magnetic technique is feasible for rapidly directing the gastroduodenal tube with ease. The technique has proved to be safe.

Thanks are extended to Dr. Elton Watkins, Jr., of the Lahey Clinic, Boston, Massachusetts, Dr. Nicandro F. DeCesare of Clover Hill Hospital, Lawrence, Massachusetts, and to Dr. Samuel Klauber of the McCarthy Clinic in Lawrence, Massachusetts for their cooperation in the performance of tests on patients.

Peritoneal tap in abdominal trauma

THEODORE DRAPANAS, M.D.
JOHN McDONALD, M.D.
BUFFALO, N. Y.
From the Department of Surgery, University of Buffalo School of Medicine, and the Edward J. Meyer Memorial Hospital

Along with the increasing incidence of traumatic lesions seen by physicians and emergency units of hospitals, the occurrence of multiple injuries after vehicular accidents has become a common problem.[4, 6] All too frequently, although a serious abdominal injury is present, it may be masked by concurrent head injury in a patient who may be unable to give an accurate history. In another patient, obvious injuries to the extremities and thorax may so detract from the symptomatology of abdominal trauma that serious delays in treatment may occur. Furthermore, the physician may be confronted with a patient so critically ill that complete diagnostic studies are not deemed advisable.

The control of hemorrhage from injured abdominal viscera continues to be the most common emergency measure to be necessitated by abdominal trauma. Williams and Zollinger,[8] in a recent review of 200 patients with abdominal trauma, state, "Eighty-eight per cent of deaths from nonpenetrating abdominal wounds were due to hemorrhage. . . . Of perhaps the most significance was a delay in diagnosis and treatment in half the patients who died."

It is apparent, therefore, that any attempts to decrease the mortality rate of abdominal trauma should be directed toward earlier diagnosis and treatment rather than improvement of surgical techniques which are fairly well standardized at the present time.

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One of the most valuable adjuncts in the diagnosis of suspected abdominal injury is the use of the so-called "peritoneal tap" or abdominal paracentesis. Despite numerous articles[1-3, 5, 7, 8] advocating acceptance of this valuable and simple diagnostic tool, some physicians continue to deplore its use, stating that it is a dangerous and ineffective procedure. Other physicians have not had adequate experience in performing this procedure or do not understand its merits or limitations.

In our institution, we have performed numerous peritoneal taps in the past 10 years, and the procedure has been an important tool in the differential diagnosis of abdominal trauma. It is the purpose of this report to present our experience and a brief review of the techniques of peritoneal tap in an attempt to emphasize the merits of this valuable procedure.

TECHNIQUE

The method of recovering fluid from the peritoneal cavity has undergone few changes in the past half century.[3] Fig. 1 depicts the sterile tray for peritoneal tap which is always available in our emergency room. Frequently, however, in a critical situation, a single sterile syringe and a long 18 or 20 gauge spinal needle will suffice. The patient, shortly after voiding or after catheterization if he is unable to void, is placed in the supine position and a rapid skin preparation is performed. We have preferred to use a dilute iodine solution followed by alco-

hol because of ready availability of these agents.

The abdomen is carefully examined and scars or other points of fixation of bowel to the abdominal wall are avoided in order to prevent penetration with the needle.

Subcutaneous skin wheals are raised at each puncture site with a 25 gauge needle and a few milliliters of a local anesthetic agent is infiltrated into the abdominal wall. Ordinarily, infiltration only of the skin and peritoneum is necessary. A long 18 or 20 gauge, short beveled spinal needle attached to a 10 ml. syringe is inserted through the abdominal wall until the peritoneum is entered, as determined by a slight "give" to the needle. Gentle suction is intermittently applied to the syringe as the needle is advanced slowly or carefully changed in position in searching for the desired fluid. If a positive tap is obtained, the needle is withdrawn and the procedure terminated. We have usually considered a minimum of 0.1 ml. of fluid as evidence of a positive tap. On occasions, when fluid other than blood is obtained, it is immediately placed in a sterile test tube for subsequent culture and also smeared on a slide for microscopic examination. If the initial tap is negative or any question of the source of the aspirated fluid arises, taps are repeated in other sites or quadrants.

Figs. 2 and 3 show the usual sites preferred for 4-quadrant or bilateral flank taps. We believe that puncture through the rectus sheath anteriorly should be condemned for 3 reasons. First, rectus sheath hematoma may result because of the course of the inferior epigastric vessels as shown. Second, the chance of needle penetration of the bowel is higher because gas-filled loops of bowel will tend to float anteriorly in an abdomen containing fluid or blood. Finally, aspiration laterally along the peritoneal gutters will increase the chances of success of the tap if only small amounts of fluid are present. In our experience, bilateral flank taps are equally as reliable as those performed in all 4 quadrants.

We have obtained a positive tap with as little as 200 ml. of blood present in the peritoneal cavity measured at the time of laparotomy. Giacobine and Siler,[3] in an excellent experimental study with dogs, showed that a 78 per cent positive tap rate can be achieved with a volume of blood comparable to 500 ml. in the average human adult.

Table I shows the accuracy of peritoneal tap reported by other authors in recent publications. A positive tap rate approximating 80 per cent can be anticipated with correct technique, and emphasizes the accuracy of this procedure.

COMPLICATIONS

Complications attendant to this procedure are rare. We have seen only 1 complication in our series and this was attributed to faulty technique resulting from puncture

Table I. *Results of peritoneal taps in recent experimental and clinical reports on abdominal trauma*

Report	*No. of cases*	*% accuracy*
Giacobine and Siler (1960)	101 patients	82
Williams and Zollinger (1959)	200 patients	79
Baxter and Williams (1960)	80 dogs	90
Economy and associates (1960)	47 patients	83
Authors' series	80 patients	82

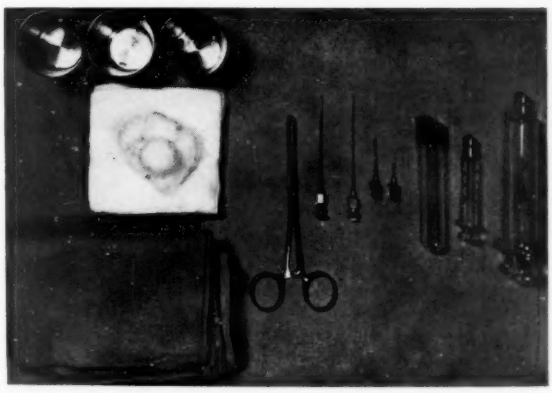

Fig. 1. Tray for abdominal paracentesis available in emergency room for immediate use.

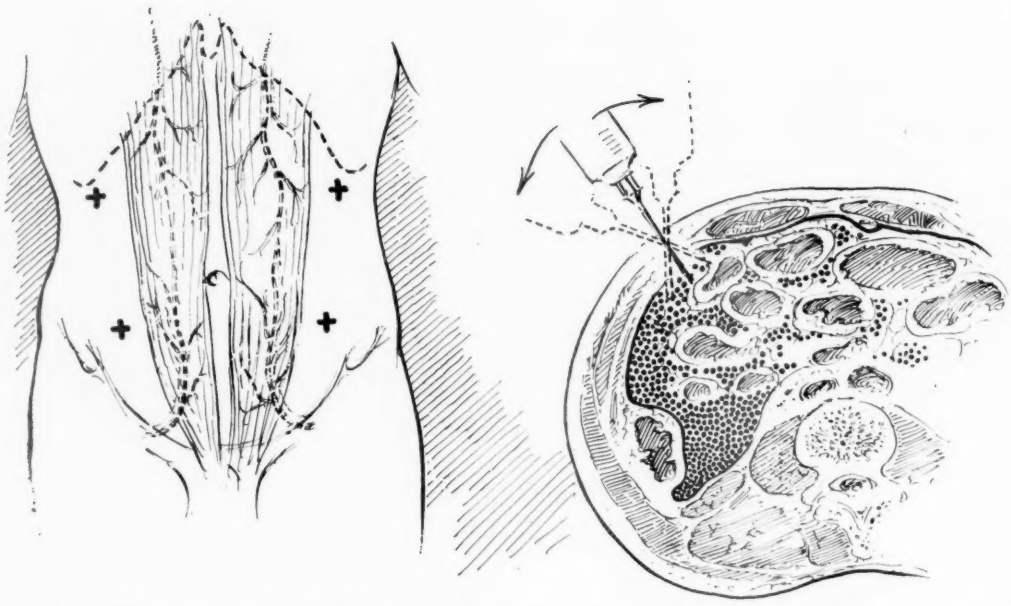

Fig. 2. Technique for 4-quadrant peritoneal taps. Preferred location for aspiration of each quadrant is shown. Note that puncture through the rectus sheath is avoided.

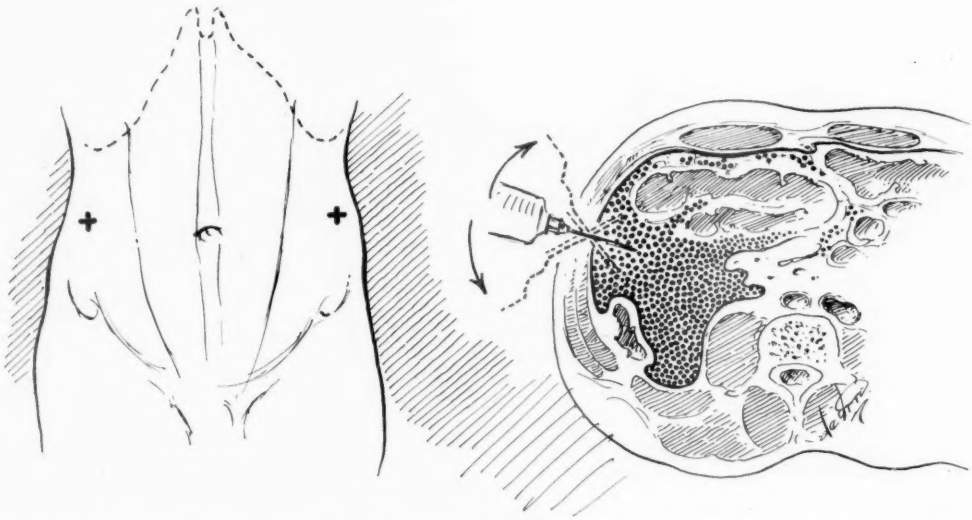

Fig. 3. Technique for bilateral flank taps. Aspiration is performed in each flank midway between costal margin and iliac spine. In our experience, bilateral flank taps are equally as reliable and more easily performed than 4-quadrant taps in cases of abdominal trauma.

through the rectus sheath and laceration of the inferior epigastric artery which necessitated subsequent drainage of a hematoma. Although in some instances bowel content was aspirated, no known complications have occurred. At subsequent laparotomy in most of the patients, no evidence of the puncture wound in the bowel causing continued leakage and requiring suture has been found. We have not considered this occurrence to be a serious drawback to the procedure inasmuch as direct puncture of the bowel with an 18 gauge needle performed during other surgical procedures rarely, if ever, requires suturing because of the self-sealing action of the bowel wall. Similar conclusions have been reached by most authors on this subject. Nevertheless, at least on theoretical

grounds, it is believed that peritoneal tap should probably be avoided in the presence of distended bowel in which the elevated intraluminal pressure may tend to cause continued leakage, even through a small needle puncture.

A careful perusal of our experience and that reported in the literature does not show any known instances of laceration of an intraperitoneal or mesenteric vessel attributed to a peritoneal tap.

Examples of the invaluable information obtained by peritoneal tap can perhaps be emphasized by case reports.

CASE REPORTS

Case 1. C. P., a 20-year-old man, was admitted 15 minutes after an accident involving an automobile which he was driving. He was unconscious and did not respond, even to painful stimuli. There was a large scalp laceration, and the pupils were unequal and responded poorly to light. The initial blood pressure was 120/75 mm. Hg, pulse rate was 120 per minute, and respirations were irregular. Breath sounds were diminished on the right and paradoxical motion of the right upper anterior chest was present. The abdomen was soft with normal peristalsis. Deep-tendon reflexes were absent in the left upper extremity, and bilateral Babinski signs were present. Chest roentgenogram showed a right pneumothorax and multiple right rib fractures. A closed-tube thoracostomy and tracheostomy were performed, resulting in marked improvement of the patient's condition. Catheterization showed a grossly bloody urine. Despite negative abdominal signs, peritoneal taps were performed in both flanks shortly after admission and these showed a free flow of blood from the right side. A transfusion was promptly started, and the patient received a total of 2,000 ml. of blood and 2,000 ml. of saline solution in the next 2 hours while the neurological status was being carefully evaluated. A laparotomy was performed, and approximately 3,000 ml. of blood found in the peritoneal cavity from a ruptured spleen and a liver laceration. Splenectomy and suture of the liver laceration were carried out. Postoperatively, the patient remained comatose for the next 4 days, then gradually regained consciousness. Lumbar puncture on the fifth day showed xanthochromic fluid. The patient's subsequent course was uncomplicated except for a residual neurological deficit in the left upper extremity related to a probable brachial plexus injury.

This case illustrates the necessity of peritoneal taps despite the absence of abdominal signs in an unconscious patient with multiple injuries. In this instance, blood replacement was rapidly instituted and operation was promptly performed to control intraperitoneal bleeding. At no time was the patient in oligemic shock. A considerable delay in diagnosis of the abdominal injury might have occurred in this patient had peritoneal taps not been so promptly performed.

Case 2. W. P., a 30-year-old woman, was admitted to the psychiatric service with acute alcoholic intoxication, tremors, and confusion. Studies in the hospital yielded a clinical diagnosis of chronic Laennec's cirrhosis with hepatosplenomegaly. Four months after admission, because of continued hepatomegaly, a needle liver biopsy was performed through the tenth intercostal space at the anterior axillary line without event. The next day because of anorexia, mild abdominal distention, and questionable tenderness in the epigastrium, surgical consultation was obtained. Blood pressure at that time was 110/70 mm. Hg and pulse was 116 per minute. Hemoglobin was 11.5 Gm. Four-quadrant peritoneal taps were performed, and 50 ml. of dark blood was obtained from the right lower quadrant. Transfusion of 1,000 ml. of blood and a laparotomy were performed. A 2 cm. laceration of the liver and 2,000 ml. of blood were found in the peritoneal cavity. Suture of the liver laceration was performed, additional transfusions were given, and the patient had an uneventful recovery.

This case, like the previous one, also emphasizes the value of diagnostic peritoneal taps in a patient with equivocal clinical signs in whom an earlier diagnosis was made and the necessity for blood replacement and operation was recognized before the appearance of clinical shock.

Case 3. J. G., a 45-year-old man, was admitted to the hospital in a disoriented state 2 hours after an automobile accident. Blood pressure was 110/80 mm. Hg and pulse was 88 per minute. Physical examination was negative except for lack of conjugate eye movement and mild upper abdominal tenderness and spasm. Hematocrit was 40 per cent. Four-quadrant peritoneal taps gave negative results. Roentgenograms of the skull and abdominal scout films were negative. Despite the negative peritoneal taps, exploratory laparotomy was performed, and a retroperitoneal laceration of the duodenum was found and repaired. No free fluid was present in the peritoneal cavity. The postoperative course was uneventful.

This case is presented to emphasize the need for abdominal exploration in a patient with abdominal signs after blunt abdominal trauma despite negative roentgenographic evidence and negative results of peritoneal taps. A negative peritoneal tap should not replace surgical judgment in this instance, for only positive taps are to be considered significant.

SUMMARY

1. Peritoneal tap is a useful, safe, and highly accurate procedure. The indications, techniques, and evaluation of results of peritoneal tap are discussed.

2. The most significant causes of death in acute abdominal trauma continue to be a delay in diagnosis and inadequate resuscitation and control of hemorrhage. It is believed that the frequent use of peritoneal tap as a diagnostic adjunct, in addition to the established surgical principles, will prevent delay and lead to earlier surgical intervention in the patient with occult intraperitoneal injury.

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Technique in resection of esophageal diverticulum

J. MURRAY BEARDSLEY, M.D.
PROVIDENCE, R. I.
From the Department of Surgery, Rhode Island Hospital

The one-stage operation for Zenker's diverticulum of the esophagus is now generally accepted as the operation of choice. Other techniques, such as suspension, inversion of the diverticulum, and the two-stage procedure, have little to recommend them. Although the one-stage operation has been generally accepted, certain refinements can be applied which will tend to ensure a more perfect end result.

The 2 main pitfalls that have long been recognized are, first, inadequate removal of the sac and, second, the danger of narrowing at the point of excision (Fig. 1). In order to avoid these 2 errors, we have for some years employed a method that has been extremely helpful to us and, in our opinion, allows the surgeon to accomplish the operation with a greater degree of perfection.

The operation is routinely carried out with a nasogastric tube in place, and some surgeons believe that as the diverticulum is being resected, the "open" method will guard against the aforementioned dangers. This is not always true since it may still be difficult to pinpoint the exact junction between the esophagus and the diverticulum, especially at the inferior border. If the slightest amount of diverticulum is left at this point, recurrence is likely. Furthermore, even with a Levin tube in the esophagus, it is still possible to angulate the esophagus as the dissection is being carried out.

After exposure of the esophagus, either through a vertical incision along the anterior border of the sternal mastoid or a curved transverse incision (we prefer the latter for cosmetic reasons), the diverticulum is identified and partially dissected out. At this stage, the anesthetist threads a McGill tube over the nasogastric tube and the surgeon gently assists its passage beyond the

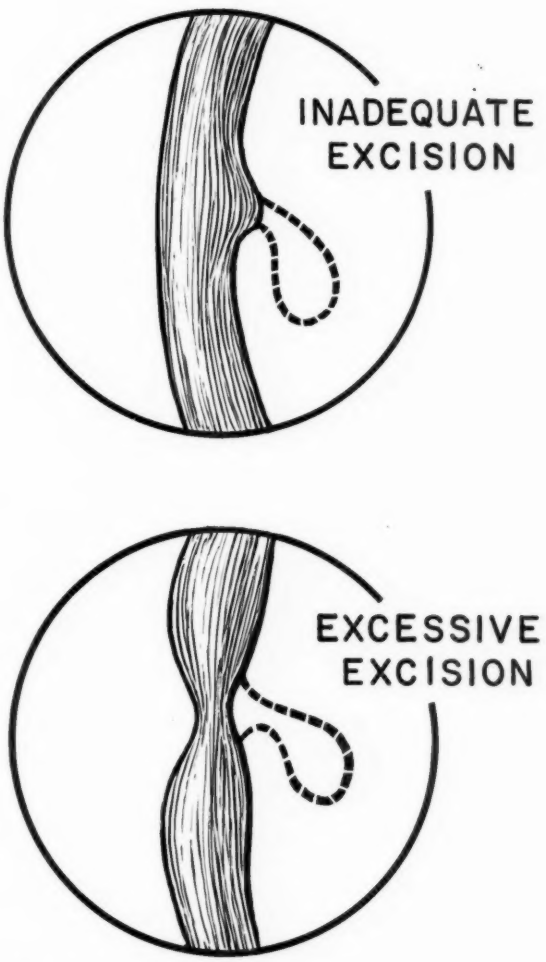

Fig. 1.

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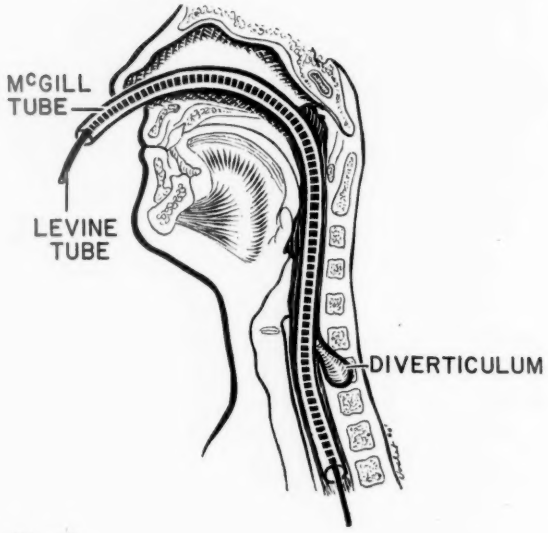

Fig. 2.

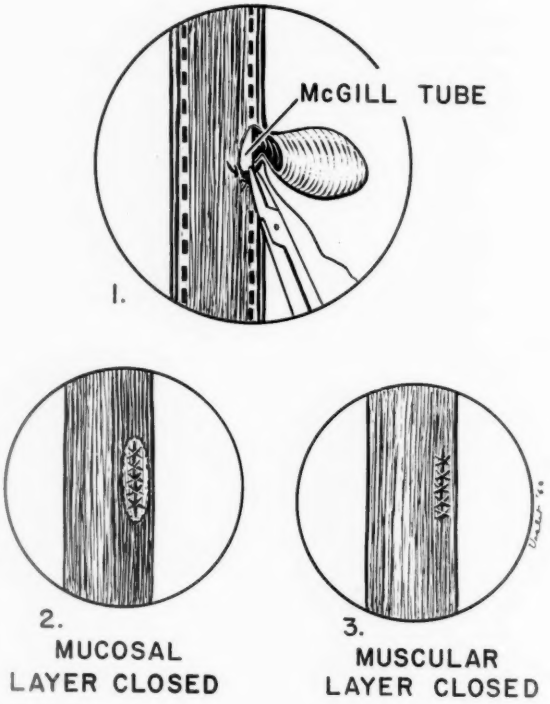

Fig. 3.

neck of the diverticulum (Fig. 2). With this wide-caliber rigid tube in place, the dissection is continued. It is now impossible to

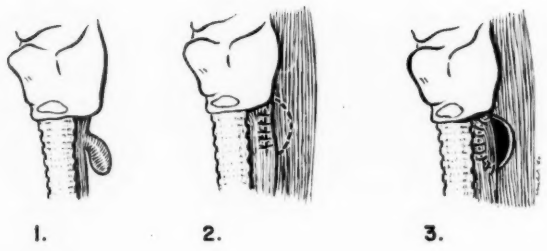

Fig. 4.

angulate the esophagus and thus narrowing is prevented. Furthermore, the normal diameter of the esophagus is demonstrated and preserved which allows a definitive dissection, excision, and closure of the mucosal layer.

No crushing instruments should ever be placed on the esophageal side. Sutures are placed as the untraumatized mucosa is cut and closed over the McGill tube. As the diverticulum is excised, closure is made with atraumatic interrupted sutures of No. 4-0 silk in a manner similar to that used in dividing and closing the bronchus. The McGill tube is visible as this step is being carried out. After closure of the mucosal layer, the McGill tube is withdrawn to allow for a relaxed closure of the muscular layer (Fig. 3).

Drains should never be placed in proximity to the suture line since this will encourage fistula formation. However, there is no real objection to placing a small rubber tissue drain 2 to 3 cm. distant from the line of suture. With the present technique, we have never had a fistula develop and, as a matter of fact, we employ drainage only occasionally.

We have continued to use a pedicle flap of prevertebral fascia as a buttress to the suture line, as previously reported (Fig. 4).

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Metastatic malignant schwannoma with bilateral pulmonary resection

K. H. RONALD CHANG, M.D.
FAUSTINO N. NIGUIDULA, M.D.
BUFFALO, N. Y.
From the Department of Health, State of New York; J. N. Adam Memorial Hospital; and the Department of Surgery, Buffalo General Hospital

Although pulmonary resection for solitary pulmonary metastatic lesions after the primary lesion has been controlled is now an established procedure, resection for multiple pulmonary metastatic nodules with bilateral involvement has been very rarely performed and, in fact, is not advocated by most thoracic surgeons. Review of the English literature up to 1959 has shown that only 12 cases have been reported in which bilateral resection for metastatic lesions were performed (Table I).

Schwannoma or neurilemmoma is generally considered to be a benign, slow-growing tumor. Malignant degeneration is very rare and only 4 documented instances have been reported.[12, 16] This rarity may be actual but the confusion in the nomenclature of this tumor may indicate that the malignant forms are more frequent. Furthermore, the embryonal origin of Schwann cells from the neural crest may make it indistinguishable from other malignant tumors of similar origin, such as sympathicoblastomas.[16]

This case is presented because (1) malignant schwannoma is very rare, (2) bilateral resection for multiple metastatic pulmonary lesions is seldom performed, and (3) the patient is alive 3 years after the first lobectomy and 2½ years after the second lobectomy.

CASE REPORT

U. D., a 64-year-old white man, had a tumor removed from the left side of the neck beneath the angle of the mandible in February, 1950. The lesion had been first discovered by the patient 3 years previously. At that time it was about the size of a pea, and by the time of excision its size had increased to that of a "small egg." The histologic picture of the resected growth was that of a neurofibrosarcoma.

In May, 1954, 4 years after the first excision, the tumor recurred, and it was removed locally. Microscopically the tissue removed showed interlacing bundles of elongated cells arranged in a plexiform manner. The nuclei were large, irregular, and hyperchromatic with an occasional mitosis. A diagnosis of malignant schwannoma was made (Fig. 1). Another local excision was performed in September, 1954, for the recurrence of a mass in the same area, but the histologic section at that time showed only granulation tissue.

Two years later, July, 1956, the patient was admitted to the Roswell Park Memorial Institute for recurrence of the growth in the left submaxillary area. The patient stated at that time that the rate of growth appeared to be faster. Excisional biopsy was carried out. The tissue removed was 3 by 2 by 1 cm. in size. The tumor mass was lobulated and encapsulated with a histologic picture similar to that present in 1954. This local excision was followed by left radical neck dissection. Although the excised lymph nodes were reported to be free of tumor, a portion of the muscle and connective tissue was found to be invaded by malignant cells. Chest roentgenograms at that time did not show any evidence of lung metastasis. The patient was followed, thereafter, at the Roswell Park Memorial Institute and no recurrence of the tumor in the neck or evidence of metastasis was noted.

The patient was next admitted to the J. N. Adam Memorial Hospital on July 8, 1957 for complaints of nonproductive cough, easy fatigue, pain in the left side of the chest, and some difficulty in swallowing. He had lost 16 pounds of weight during the preceding 6 months, and a chest roentgenogram made shortly before admission showed an abnormal shadow in the left lung field (Fig. 2). The patient had been smoking 1

Table I. *Reported cases of bilateral pulmonary resection for metastatic lesions*

Year	*Author*	*Lesion*	*Procedure*	*Interval**		*Remarks*
				1	*2*	
1940	Churchill[4]	——	Bilateral partial lobectomy	—	—	No details
1947	Alexander[1, 2]	Spindle-cell neurosarcoma	Bilateral lobectomy	1 yr.	1 yr.	Alive after 9½ yr.
1951	Ehrenhaft[6]	Leiomyosarcoma	Resection of lingula	46 mo.	2 mo.	Died 6 mo. after lung operation, 4½ yr. after primary operation
1955	Higginson[8]	Teratocarcinoma	(1) Multiple segment, right, (2) multiple segment, left, (3) segment, left lower lobe	23 mo.	2 wk. 6 mo.	8 mo. after lung operation had left nephrectomy and adrenalectomy, died
1955	Higginson[8]	Adenocarcinoma of stomach	(1) Left lower lobectomy, (2) segment, right lower lobe	45 mo.	17 mo.	Only 3 mo. follow-up with no recurrence
1955	Jones[10]	Malignant melanoma	(1) Lower lobectomy, (2) lower lobectomy	8 yr.	8 mo.	Died 7 mo. after second lobectomy
1955	Weinberg[21]	Osteosarcoma of femur; had hemipelvectomy	Local excision	Few months		No follow-up
1956	Groves and Effler[7]	Hemangiopericytoma of skin of back	(1) Local excision, (2) local excision, right lung	13 yr.	2 yr.	No follow-up
1956	Groves and Effler[7]	Hemangiopericytoma of femur	(1) Local excision, left upper lobe, (2) local excision, right upper lobe	1 yr.	14 mo.	1½ yr., no recurrence
1956	Strieder[19]	Adenocarcinoma of colon	(1) Right upper lobectomy, (2) left lower lobectomy	1 yr.	7 mo.	Died 2 yr. later
1956	Strieder[19]	Adenocarcinoma of colon	(1) Segment, left upper lobe, (2) left upper lobectomy	5 yr.	4 yr.	Alive 71 mo. after second operation
1959	Rumel[16]	Osteogenic sarcoma	(1) Right middle lobectomy, (2) left lower lobectomy and lingulectomy	—	3 wk.	7-year "cure"
1960	Chang	Malignant schwannoma	(1) Right upper lobectomy, (2) right upper lobectomy	6 yr.	10 mo.	3 years, alive

*1, Interval between removal of primary lesion and first pulmonary resection. 2, Interval between the 2 pulmonary resections.

pack of cigarettes per day for the past 48 years. He had worked as a farmer and later as a buffer in a tanning factory. He had resided almost exclusively in western New York.

Physical examination on admission showed him to be a well-developed, fairly well-nourished white man in no acute respiratory distress. The temperature was normal. There was a healed incisional scar in the left submandibular area. The lungs were clear to auscultation and percussion. The results of a tuberculin test and sputum examinations for tumor cells were negative. Several 24- and 72-hour sputum specimens were negative for the presence of acid-fast bacilli when studied by the concentration and culture methods.

Chest roentgenograms showed an abnormal density located anteriorly in the left upper lobe. No cavity was demonstrated in planigraphic views. Bronchoscopy and bronchograms failed to show signs of any endobronchial disease. The planigrams showed 2 separate, fairly discrete shadows with surrounding haziness.

On Aug. 20, 1957, a left thoracotomy was performed. The palpable and visible disease was limited to the left upper lobe and consisted of a dimpling and retraction at the junction of the anterior and apicoposterior segments. A hard irregular mass, measuring 3 by 4 cm., was first removed by wedge excision but when the frozen section showed malignant schwannoma a left upper lobe lobectomy was performed (Fig. 3). The thickened area in the operative scar of the neck was likewise excised a few days later, but was found to be free of tumor on microscopic examination.

The patient was then followed in the Outpatient Department and monthly chest roentgenograms did not show any change until 8 months later when new disease was seen in the right upper lobe (Fig. 4). By this time, the patient had again developed a cough, but it was productive of 30 to 100 ml. of mucoid sputum per day. He was readmitted to the J. N. Adam Memorial Hospital on April 24, 1958. Physical examination yielded essentially negative results. Results of tuberculin and histoplasmin skin tests were negative. The sputum was negative for acid-fast bacilli and tumor cells. Pulmonary function studies showed a maximum breathing capacity of 47 L. and a vital capacity of 2,850 ml., or 74 per cent of predicted normal. On May 26, 1958, a right upper lobe lobectomy was performed. The resected lobe contained 3 large nodules, 1 in the apical segment, a smaller one in the anterior segment, and another small one at the junction of the anterior and posterior segments. Microscopic sections showed involvement of the subpleural parenchyma and also the overlying pleura. The cells were long and spindle-shaped, arranged in interlacing bundles with tendency to palisade. The nuclei varied in size and shape, and there were as many as 7 mitotic figures per high power field (Fig. 5). The postoperative course was complicated by an auricular fibrillation which responded to digitoxin and quinidine. Since discharge from the hospital on July 11, 1958, the patient has been followed in the Outpatient Department. He has maintained his weight at around 170 pounds. He complains only of moderate dyspnea on exertion which he claims prevents him from any gainful occupation. Serial chest roentgenograms have not shown significant change or evidence of a new lesion (Fig. 6).

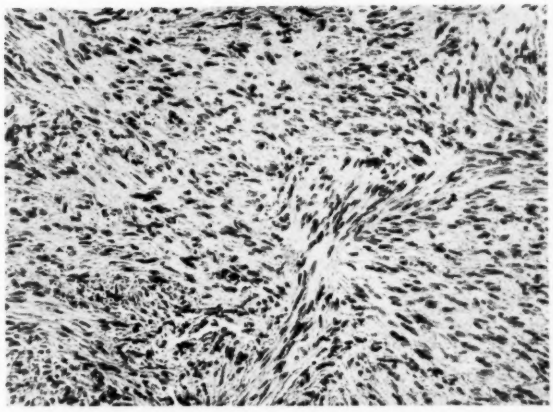

Fig. 1. Section from the original lesion from left side of neck shows interlacing bundles of elongated cells arranged in plexiform manner. The nuclei are large, irregular, and hyperchromatic with occasional mitosis. (Hematoxylin and eosin; ×100; reduced 4/7.)

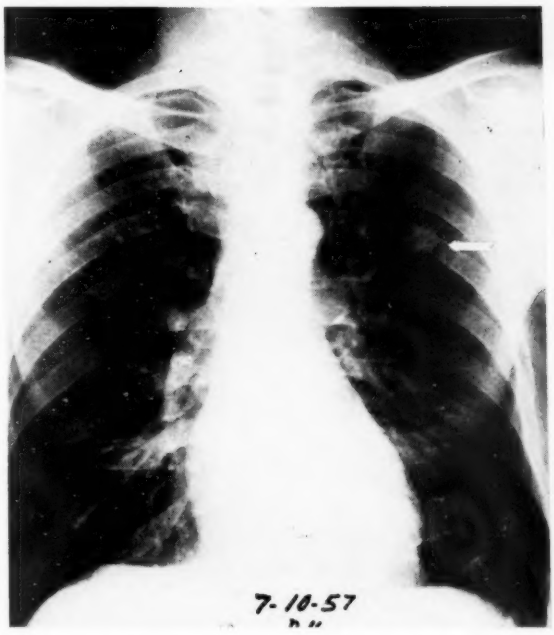

Fig. 2. Chest roentgenogram taken in 1957 shows the lesion in the left upper lung field.

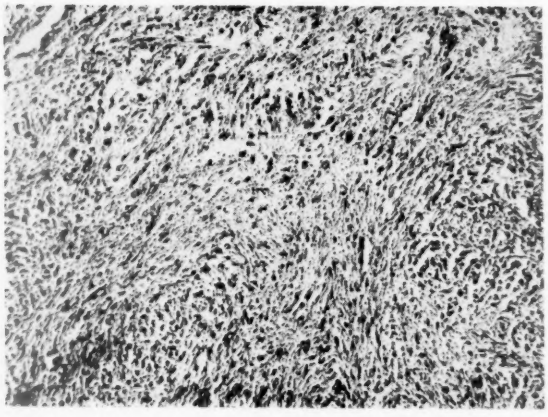

Fig. 3. Microscopic section of the lesion removed from the left upper lobe shows a very similar pattern to that seen in Fig. 1. (Hematoxylin and eosin; ×100; reduced 4/7.)

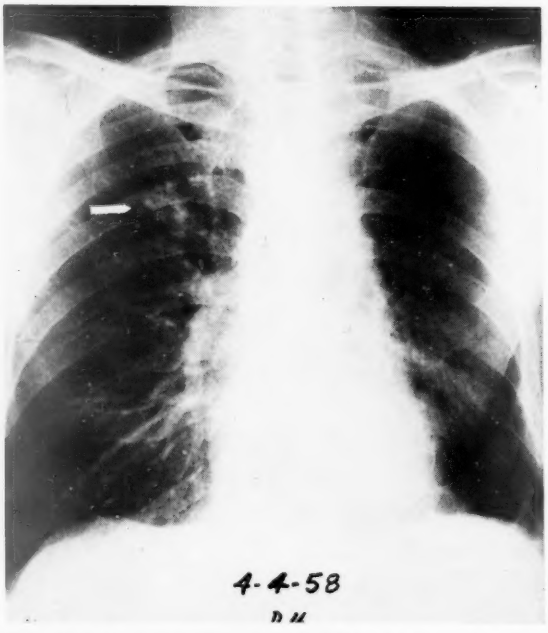

Fig. 4. Chest roentgenogram taken 8 months after the first film shows new disease in the right upper lung field.

DISCUSSION

Robinson, in a recent survey of all the thoracic surgeons in the United States, found that 91.8 per cent, or a total of 279, of the responding surgeons resect solitary pulmonary metastatic lesions.[15] Although not openly admitted, resection for metastatic lesions, when the primary site has been controlled, is now widely practiced and even recommended as an advisable procedure. The extent of resection advocated is very limited and in most cases is performed in the guise of palliation.

In the majority of cases the removal of a solitary pulmonary nodule is motivated by the absence of a definite diagnosis. The appearance of a nodule in the lung sometime after removal of an extrapulmonary malignancy is no indication that it is necessarily metastatic. The chance of its being another primary lesion is from 3.2[3] to 4.1 per cent.[13] Several authors have set criteria for differentiating a metastatic nodule from a primary lesion, but even this is not helpful to the surgeon, who usually has to make the final decisions as to whether or not thoracotomy should be performed.[5-11]

The lung is the second most common site of metastatic lesions for most malignancies.[14] Pulmonary metastases result from embolization after tumor invasion of the regional veins at the primary site.[16] If the primary growth had been completely controlled, no further embolization and lung involvement need be expected. In 18.3 per cent of lung metastases, there is an invasion of the bronchial wall. It is therefore very likely that further spread in the lung from the metastatic focus can be accomplished by both hematologic and bronchogenic pathways.[14] Coexistent multiple metastatic foci need not necessarily arise from the original extrapulmonary primary focus.

In the majority of cases reported, there was a time interval between the appearance of the various lung lesions. Removal of 1 focus and subsequent appearance of another focus again raises the possibility of the latter nodule being a primary tumor. Again, thoracotomy is performed mainly for diagnosis and secondly for prevention of complications such as hemoptysis, bronchial obstruction, and suppuration. The morbidity and mortality rate for exploratory thoracotomy has now been reduced to a minimum so that even for palliative purposes, resection may be offered.

Analysis of the 12 reported cases and our case, in which bilateral resections have been performed, showed no correlation between

the type of tumor and the length of survival period after pulmonary resection. Six of the 13 patients (46 per cent) survived over 1 year after the second operation, whereas the survival rate for 1 year and over after pulmonary resection for unilateral metastatic lesion is 75 per cent.[19]

SUMMARY AND CONCLUSION

A case of a 64-year-old white man who underwent bilateral lobectomy for metastatic pulmonary lesions arising from a previously removed malignant schwannoma of the neck is presented. The patient is alive and well 2½ years after bilateral pulmonary resection. Malignant degeneration of schwannoma (neurilemmoma) is very rare. Bilateral pulmonary resection for metastatic lesions is occasionally performed and, so far, only 12 cases are reported in the English literature.

Resection for multiple metastatic lesions in the lung, when the removal is surgically feasible and will not incapacitate the patient, appears to be justified in certain selected cases not only for palliation, but also in hope of cure.

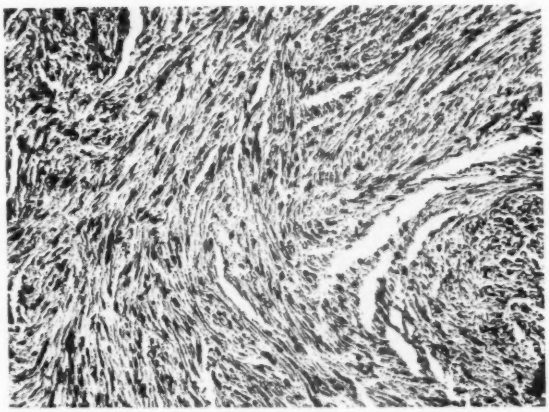

Fig. 5. Section from the right upper lobe. The cells are long and spindle shaped, arranged in interlacing bundles with tendency to palisades. The nuclei vary in size and shape and there are numerous mitotic figures. (Hematoxylin and eosin; ×100; reduced 4/5.)

Fig. 6. Roentgenogram taken in June, 1960, shows no recurrence and no new disease.

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Anuria after operation for abdominal aortic aneurysm treated by hemodialysis with complete recovery

JÖRGEN HINDBERG, M.D.
SATORU NAKAMOTO, M.D.
WILLEM J. KOLFF, M.D.
CLEVELAND, OHIO
From the Department of Artificial Organs and Division of Research, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute

Acute renal failure is one of the common and most severe complications of grafting of the aorta, and it is often the direct cause of death. Anuria after aortic operations may be due to any of 5 causes.

First, emboli of atheromatous material may be whirled up the clamped part of the aorta and lodged in the renal arteries.[5] This is the most frequent cause of anuria and is almost always fatal,* but it occurs less frequently in patients who are handled by experienced surgeons.

Second, ischemia due to low blood volume, shock, and temporary occlusion of renal vessels may result in acute tubular necrosis.

Third, blood transfusion accidents or overheating of cold blood may cause hemoglobinuric tubular damage.

Fourth, tubular damage occurs more often when a large number of transfusions have been given, and also when necrosis of an extremity is present. It is likely that sludging of blood may play a role in the pathogenesis of this type of tubular damage.

Fifth, anuria may result from a combination of the factors described. An excellent review of the pathogenesis of renal failure after aortic operations has recently been given by Doolan and associates.[1]

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*We saw 6 of these occurrences in 1 year, but have never seen one originate among the patients operated on at the Cleveland Clinic.[2, 3]

CASE REPORT

A 54-year-old man who had suffered increasingly severe lumbar pain for a period of 9 months was found to have a large abdominal aortic aneurysm. A Dacron aortic graft was inserted. The aneurysm extended from the immediate subrenal level to the bifurcation of the aorta with calcification of the aortic wall and the common iliac arteries. The operation lasted over 9 hours and was difficult because of an unusual amount of adhesions and dense inflammatory connective tissue around the aneurysm. Lacerations of the right renal artery and the left renal vein occurred. The right renal artery had to be reanastomosed so that the right kidney was without a blood supply for approximately 90 minutes. The left renal vein, being obstructed for approximately 4 hours, was replaced by a venous autograft taken from the saphenous vein. After operation, there were good pulsations in both femoral and pedal arteries. During the operation 7 pints of whole blood and 1 pint of plasma were given to the patient. There was no evidence of incompatibility.

Postoperatively, the patient was given Levophed and Sol-Cortef for 2 days. He was also treated with cortisone, calcium gluconate, and Aureomycin, because of the need to maintain the blood pressure with vasopressors. Daily fluid intake was about 2 L. Immediately after the operation he developed severe oliguria with a daily urinary output of less than 150 ml. The blood urea level increased to 104 mg. per 100 ml. on the third day; serum creatinine reached 13 mg. per 100 ml.; carbon dioxide content was 22 mEq. per liter, serum potassium, 5.8 mEq. per liter; and sodium, 134 mEq. per liter.

The patient was tranferred to the Cleveland Clinic Hospital on the fourth postoperative day for evaluation and treatment with the artificial kidney.[4] Upon admission to the Clinic, he was alert

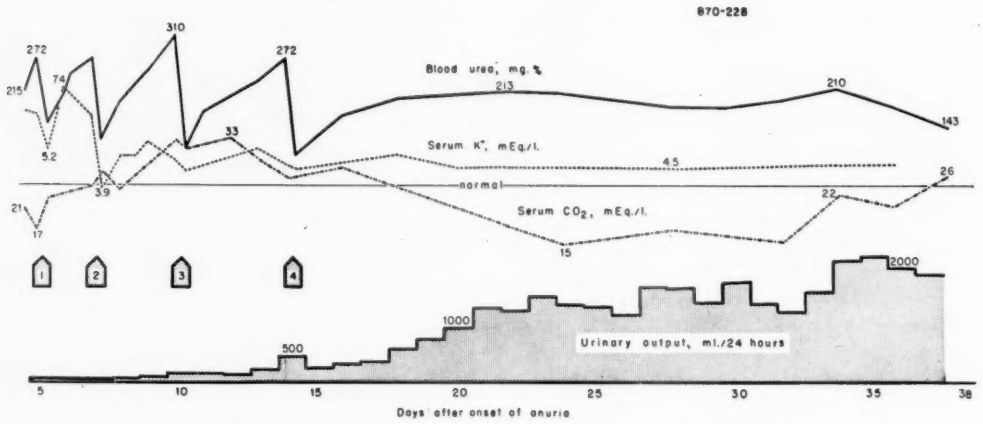

Fig. 1. The course of blood urea, serum potassium, and carbon dioxide content in patient with renal shutdown after aortic grafting operation. The horizontal line indicates the normal level of blood urea, serum potassium, and carbon dioxide content. Note the drop in blood urea at each of the 4 dialyses. Also note that a urine volume between 1,000 and 2,000 ml. was not sufficient to lower the blood urea level to under 200 mg. per 100 ml. Six months after discharge, blood urea level was 52 mg. per 100 ml., serum potassium level 4.8 mEq. per liter, and carbon dioxide content 23 mEq. per liter.

and cooperative. The skin was somewhat dry, but pulmonary or peripheral edema was not evident. The abdomen was rather distended but peristalsis was active. The serum electrolytes were sodium, 136; potassium, 6.6; chloride, 94; and carbon dioxide, 21 mEq. per liter. The hemoglobin count was 14.1 Gm. per 100 ml., and cell volume, 43 per cent. The blood urea level was 215 mg. per 100 ml. On the fifth postoperative day, the patient underwent treatment with the artificial twin-coil kidney* for 3 hours.[4] The blood urea level decreased from 272 to 158 mg. per 100 ml. and creatinine from 13.6 to 10.0 mg. per 100 ml.

Because the patient was oliguric until the seventeenth postoperative day, he was treated with the artificial kidney 4 times. Corrections of electrolytes and lowering of retention products were obtained each time (Fig. 1). The daily urinary output was slowly increasing, and after 34 days it was more than 2,000 ml. per 24 hours. The blood urea level was reduced to 104 mg. per 100 ml. at the end of the fourth hemodialysis, rose to 213 mg. per 100 ml., then was stabilized at around 200 mg. per 100 ml. for 2½ weeks, and finally started to decrease. On the day of discharge, the thirty-eighth postoperative day, the blood urea level was 143 mg. per 100 ml. The recovery was uneventful except for a slight fever (90° to 101° F.) from the eighth to the thirty-first postoperative day which was treated with antibiotics. A pleural effusion present from the twenty-second to the twenty-sixth postoperative day was treated with thoracentesis with removal of a total of 1,800 ml. of transudate. The patient was in excellent condition when examined 6 months after operation. He had a normal blood urea level and apparently was fully recovered.

*Travenol Laboratories, Inc., Morton Grove, Ill.

DISCUSSION

The case report illustrates the importance of intensive treatment of acute renal failure which follows anuria after vascular operations. The patient was oliguric for 17 days and did not reach a daily urinary output of 2,000 ml. until the thirty-fourth postoperative day.

Therapy in cases of acute renal failure should include a general supportive program with a high caloric, low protein diet, large doses of vitamins, and the restriction of certain electrolytes such as sodium and potassium. Administration of fluid is based upon a daily record of body weight and fluid intake and output, and more than 700 ml. per 24 hours is rarely given during the anuric phase, although compensation can be made for both fluid and electrolyte losses. Frequent dialyses with ultrafiltration greatly facilitate fluid and electrolyte management. Administration of antibiotics is desirable in the prevention and treatment of infections. Treatment with the artificial kidney is indicated if the blood urea level is greater than 200 mg. per 100 ml., if serum potassium exceeds 7 mEq. per liter,

if plasma carbon dioxide content is less than 12 mEq. per liter, or if the clinical condition of the patient deteriorates.

Our present policy is to dialyze frequently in the hope that the patient can avoid the clinical symptoms of uremia and that he can be left in optimum clinical condition so that he can eat better, his wounds can heal faster, and he can be ambulated. Recovery of renal function is thus made more comfortable.

In the diuretic phase which follows the oliguria, the fluid and electrolytes are replaced at a slower rate than that at which they are excreted. Nearly all the patients lose weight during this period, which indicates that they are actually overhydrated.

SUMMARY

A case is presented of acute renal failure after an abdominal aortic operation. The patient required 4 treatments with the artificial twin-coil kidney.

Early and frequently repeated dialyses offer the best possible way for patients to recover from renal failure after operations on the aorta. Such treatment should continue as long as there is a chance for recovery and occlusion of the renal arteries or other irreparable renal damage has not been proved to be present.

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Temperature gradients associated with extracorporeal perfusion and profound hypothermia

BERNARD FISHER, M.D.
E. J. FEDOR, PH.D.
J. W. SMITH, M.D.
PITTSBURGH, PA.
From the Department of Surgery, Laboratory of Surgical Research, University of Pittsburgh School of Medicine

It is now recognized that thermal gradients which exist in the body under normal conditions become more pronounced with the induction of hypothermia.[1, 6, 13, 20] Most of the available data have been obtained when surface cooling was employed. In 1948, Haterius and Mason[9] noted as much as 3° C. difference between the liver and rectum of dogs so cooled. Hegnauer and Penrod[11] reported a brain temperature higher than that of the rectum, with the heart intermediate, and other investigators[5, 22] have demonstrated that the temperature in the rectum is usually several degrees lower than that in the esophagus. Differences of several degrees have been recorded[21] between rectum, muscle, and subcutaneous tissue when animals were cooled to 25° C.

While such variations in internal body temperature have been noted to occur with the use of extracorporeal perfusion and direct blood cooling,[4, 8, 18, 22] detailed data are lacking. This study was undertaken to obtain more knowledge of these temperature differences.

METHODS

Mongrel dogs of both sexes, averaging 14 kilograms in weight, were anesthetized with pentobarbital sodium attached to a Medtronic automatic respirator, an extracorporeal system consisting of a T. M.-2 Sigmamotor perfusion pump, a 13 inch Kay-Cross convoluted disc oxygenator, and a gas type heat exchanger.[15] The unit was primed with heparinized blood. Vascular connections were made with catheters which had been inserted via a femoral artery into the aorta at the level of the renal arteries and through the femoral and jugular veins into the venae cavae. In 1 group of dogs, prior to cooling and after laparotomy and thoracotomy, copper Constantan thermocouples* were implanted at various sites throughout the body. In other groups they were inserted at different positions within the same organ and temperatures were compared with those recorded from the esophageal thermocouple which was always placed at midesophagus. Animals were sacrificed at the conclusion of each experiment, and the precise position of the thermocouples was confirmed. A Leeds-Northrup Speedomax type G recorder, which registered automatically every 30 seconds, was used to monitor temperatures. Temperature variations as slight as 0.1° C. were detectable. A perfusion rate of approximately 50 ml. per kilogram per minute was maintained during cooling and rewarming. Rewarming was begun when the esophageal temperature registered 10° C., and perfusion was stopped when this temperature reached 25° to 30° C.

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*Type NN-30-DT Cu-Constantan-30 gauge BNS, nylon insulation, Thermo Electric Co., Inc., Saddle Brook, N. J.

RESULTS

Body thermal gradients. Probes were placed in various locations in 10 dogs, and temperatures simultaneously recorded. To facilitate presentation, temperature curves obtained have been divided in Fig. 1, *A* and *B*. It is apparent from these illustrations (which represent mean values) that a considerable thermal gradient occurs from site to site during cooling and rewarming.

Six minutes after inception of cooling, when the esophageal temperature registered 24.3 ± 3.7° C., values ranged from 31.4 ± 2.4° C. (subcutaneous) to 24.7 ± 3.5° C. (liver). With further cooling, the spread increased. Just prior to rewarming (esophageal 9.0 ± 1.0° C.), temperatures from all locations lay between 8.2 ± 2.3° C. (liver) and 18.0 ± 2.0° C. (subcutaneous). A fairly constant thermal relationship between the various sites was observed during the cooling phase. It is evident that the liver temperature more closely approximated the esophageal temperature than did that from any other site.

The esophageal temperature fell more rapidly and to a greater extreme than any of the others recorded during cooling, and upon rewarming became the most elevated. The liver temperature continued its esophageal relationship. Aside from the latter, however, no similar correlations could be established during the rewarming phase. A remarkable temperature gradient was maintained even to the time of cessation of perfusion. At this point the esophageal temperature was 30.7 ± 1.2° C., and the spleen had failed to rise above 25.6 ± 2.4° C.

Organ thermal gradients.

Brain. That all parts of the brain do not cool and rewarm similarly may be seen in Fig. 2, *A* and *B*. For clarity of presentation, brain area temperatures which approximated each other throughout within less than 1 degree were averaged and plotted as 1 curve. In all instances, temperature differentials were accentuated as cooling progressed. In the animals studied the esophageal temperature was lower—sometimes as much as 3° C. —than that recorded from the area of the brain with the lowest temperature (usually the base of the brain). Temperature gradient between the esophagus and other areas was as much as 10° C., as exemplified in Fig. 2, *A* (occipital lobes and esophagus). No consistent temperature relationship existed between the various areas of the brain. Areas which cooled most rapidly were most readily rewarmed. Occasionally, when the esophageal temperature approximated 30° C., temperatures of certain areas of the brain remained depressed (Fig. 2, *B*).

Heart. Data were obtained from 14 dogs in which thermocouples were inserted into various sites in the right and left sides of the heart. A composite of the results obtained from the right and left ventricular myocardia and chambers (mean with standard deviation), (Table I) suggests that no significant gradient in temperature occurred

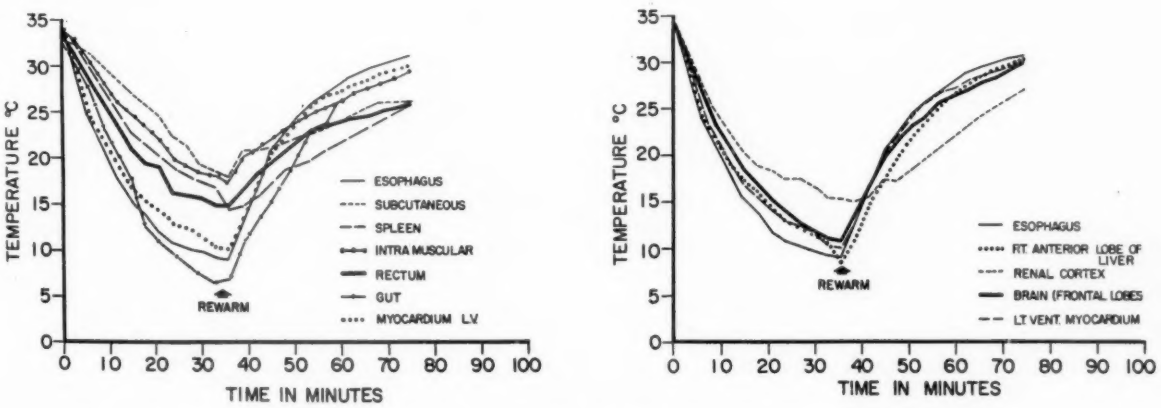

Fig. 1. Temperature variations in dogs subjected to extracorporeal cooling and rewarming. Each curve represents the mean of 10 animals.

Table I. *Mean temperatures from various parts of hearts of 14 dogs*

Position of thermocouple	*Time of extracorporeal Cooling (C.)*				
	0	*3*	*6*	*12*	*18*
Esophagus	34.1	29.7	24.1	18.6	14.0
	(1.2)	(2.5)	(3.7)	(3.0)	(2.6)
Right ventricle (chamber)	34.2	30.2	23.6	18.2	14.9
	(0.9)	(1.7)	(3.6)	(4.7)	(4.1)
Right ventricle (myocardium)	33.3	31.0	25.0	18.7	14.6
	(0.4)	(1.4)	(2.6)	(4.3)	(4.4)
Left ventricle (chamber)	34.3	30.8	24.7	18.4	14.9
	(0.7)	(1.8)	(4.1)	(5.1)	(5.2)
Left ventricle (myocardium)	34.5	30.4	24.6	19.1	15.4
	(0.8)	(1.8)	(3.3)	(4.4)	(4.4)

Numbers in parentheses indicate standard deviation.

from one region to another and between heart and esophagus. From Fig. 3, *A, B,* and *C* it may be seen that such data are misleading. Actually, cardiac gradients—in some instances quite marked—were present in every dog studied. Temperature differences were more apparent as the body temperature was lowered. Similar gradations persisted during the entire rewarming phase. No constant temperature relationship was found to exist between the esophagus and the various parts of the heart. As the temperature was reduced the gradient between the two became more pronounced, so that, for example, in some animals at 10° C. the esophageal temperature was as markedly different as ± 5° C.

Liver. In some animals there was a marked temperature gradient between different lobes of the liver which, as in the other organs, became more pronounced as cooling progressed (Fig. 4, *A*). In others (Fig. 4, *B*), less of a differential was observed. But in no animal was cooling and rewarming uniform throughout the liver.

Kidney. In 6 animals thermocouples were placed in the renal cortex, medulla, pelvis, artery and vein, and beneath the capsule. Temperature gradients at once became apparent upon cooling (Fig. 5), the greatest differences being observed just prior to rewarming when the esophageal temperature was 9.2 ± 1.3° C. At that time the renal cortex was 15.2 ± 1.5° C., the medulla 11.5 ± 2.0° C., the subcapsular area 11.9 ± 2.4° C., and the renal pelvis 8.6 ± 1.3° C. The renal artery temperature, which was similar to that of the blood entering the aorta, was 3.6° C. lower than that noted in the renal vein. A marked lag in rewarming of the kidney was apparent, but the gradients between capsule, cortex, and medulla observed during cooling diminished. At cessation of perfusion, when the esophageal temperature (30.2° C.) approximated that of the renal artery (31.4° C.), the renal cortical and medullary temperatures were still depressed (27.0° C.).

DISCUSSION

It is readily apparent from this study that with the use of extracorporeal perfusion in the production of hypothermia uniform body cooling does not occur. Marked differences in temperature exist not only from one area of the body to the other, but also within each organ. With progressive reduction of body temperature to more profound levels (10° C.) such variances become further accentuated. The more rapid the cooling and rewarming (that is, with use of increased flow rates), the greater these differentials become. While it is generally accepted[20] that in hypothermia use of the rectal temperature as an index of temperature throughout the rest of the body may be inaccurate, it seems that the same is true for temperature recorded from the esophagus.

Temperature differences from various parts of the heart during cooling and rewarming were interesting. Aside from spec-

perfusion (min.)			*Rewarming (C.)*					
24	*30*	*36*	*3*	*6*	*12*	*18*	*30*	*39*
11.9	10.5	9.2	11.9	16.8	21.9	25.2	28.6	30.3
(2.0)	(1.5)	(1.8)	(3.3)	(3.2)	(3.0)	(2.5)	(1.3)	(1.5)
12.5	11.4	9.8	13.5	17.7	23.7	26.6	29.5	30.2
(3.5)	(3.0)	(3.1)	(2.3)	(3.4)	(3.3)	(2.7)	(1.4)	(0.7)
12.8	11.5	10.8	12.9	17.5	24.1	26.5	29.5	29.1
(3.4)	(2.8)	(2.4)	(2.4)	(3.7)	(3.9)	(3.2)	(1.7)	(1.0)
12.3	10.2	9.6	12.0	15.4	20.4	24.4	28.2	29.6
(3.9)	(3.1)	(2.6)	(2.5)	(3.7)	(4.3)	(4.4)	(2.3)	(1.5)
12.9	11.5	10.1	13.0	16.7	22.0	25.6	28.4	29.9
(3.5)	(3.1)	(3.0)	(2.4)	(3.6)	(4.3)	(3.0)	(1.0)	(1.1)

ulation that such gradients might be responsible for fibrillation in hypothermia,[3, 11] no experimental evidence had been presented to confirm or deny this. Recently it was reported by us[7] that no relationship exists between such thermal differentials and the production of ventricular fibrillation encountered in hypothermia. In some animals during cooling and rewarming temperature variations in the heart as great as 10° C. were found. While fibrillation was not usually encountered under such circumstances, it was observed when little or no temperature gradient was recorded.

The marked difference in brain and esophageal temperatures found by us and others[16, 17, 23] and the variations from one portion of the brain to another may well explain the neurological sequelae occasionally observed with circulatory arrest of a protracted period when the esophageal temperature is used as an index of depth of hypothermia. In practically all of the animals the temperature in the frontal lobes lagged the most from that of the esophagus, while the probe at the base of the brain registered temperatures closest to that of the esophagus.

Our observation that the renal cortical temperature was consistently higher than that of the medulla and kidney pelvis and that a difference existed in the temperatures of the renal arterial and venous blood suggests that total kidney perfusion does not take place, but that precortical arteriovenous shunts are in effect. Likewise, as evidenced by the differences in temperature between the various lobes, uniform perfusion of the liver does not always occur. A most likely explanation for all of the thermal gradients which vary from animal to animal rests on the premise that there is a difference

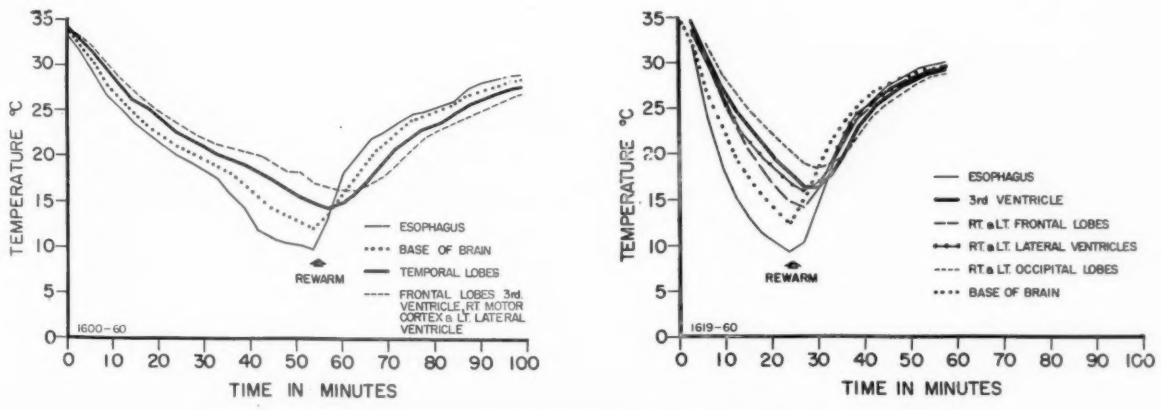

Fig. 2. Temperature differentials recorded from various parts of the brain.

in blood flow through various parts of the body. This in turn is probably related to catheter position, pump flow rates, and other as yet undescribed hemodynamic changes. Consequent to the blood flow and thermal variances, it is reasonable to assume that significant oxygen gradients likewise exist.

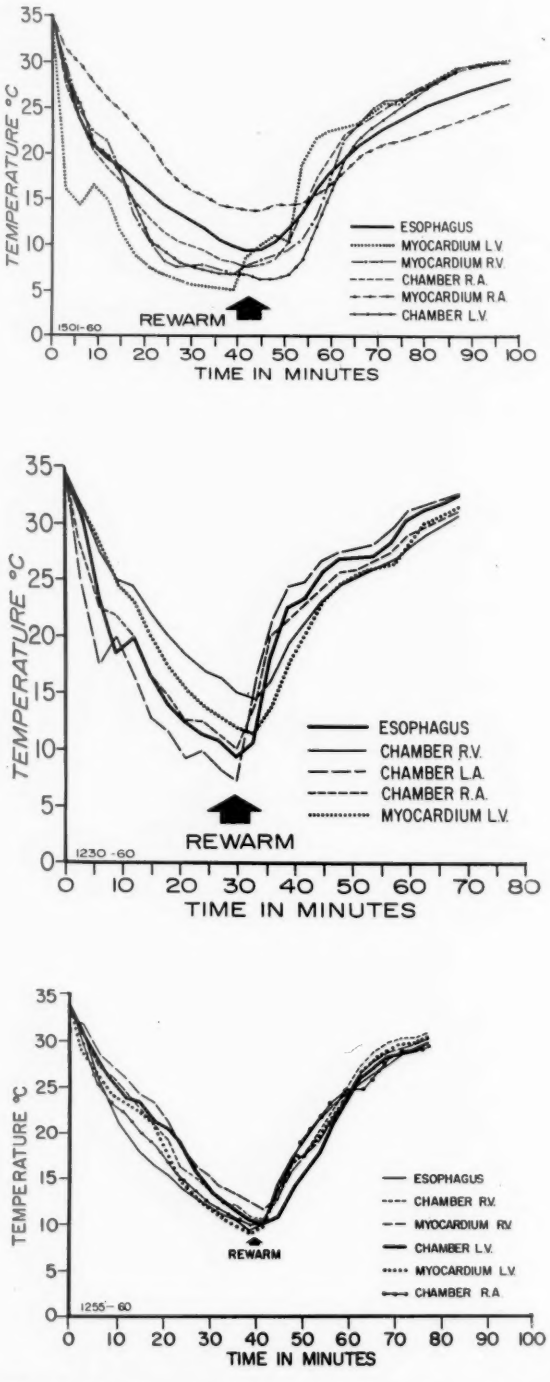

Fig. 3. Cardiac temperature gradients from 3 representative animals.

Certainly, one of the practical objectives of profound hypothermia is to permit prolonged circulatory arrest. This is feasible only if oxygen requirements at these low temperatures are markedly reduced and are adequately met. Bigelow and associates,[2] using surface cooling, reported an almost linear relationship between oxygen consumption and temperature to 20° C. when the former was 15 per cent of normal. By extrapolation of the curve, they concluded that at 10 to 12° C. oxygen consumption would be minimal. Results with extracorporeal cooling apparently are not similar. Heimbecker and associates[12] reported a variation of oxygen requirements of from 0.6 to 20 per cent of basal in 7 dogs with body temperatures between 8.5 and 12° C. when flow rates were about 65 ml. per kilogram per minute. In a recent study, Kameya and colleagues,[14] reported that at 10° C., with a flow rate of 60 ml. per kilogram per minute, oxygen consumption was 1.2 ml. per kilogram per minute, or about 17 per cent of that in monothermic animals at equivalent flow rates, but that with lower perfusion rates oxygen debt may occur. Sealy and his colleagues[19] found oxygen consumption at 20° C. to be 20 to 25 per cent of normal, while at 10° C. they believed it might be 10 per cent of normal. They also reported that after extracorporeal cooling to profound levels, circulatory arrest of 1 hour resulted in a 70 to 80 per cent reduction of oxygen in mixed venous blood with an oxygen debt occurring.

It may well be assumed from this evidence of continued substantial oxygen consumption at such profound levels of cooling that, due to lack of uniform cooling, oxygen debt in certain tissues may be more profound than in others, and that frank damage due to anoxia may result. If further prolongation of circulatory arrest in the profoundly cooled man or animal is contemplated, it seems that effort should be expended to obtain more uniform cooling.

SUMMARY

The use of extracorporeal perfusion and heat exchange to produce profound hypo-

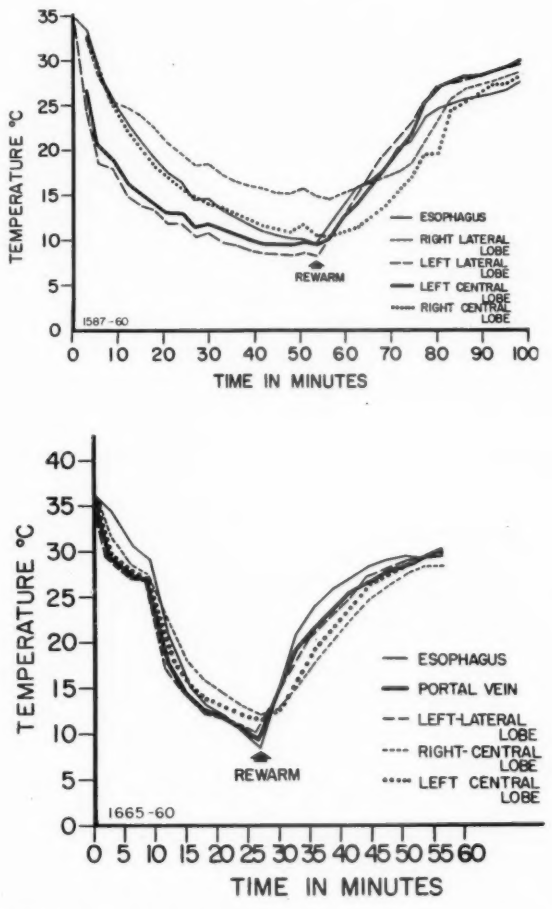

Fig. 4. Characteristic temperature variations in the liver after extracorporeal cooling and rewarming.

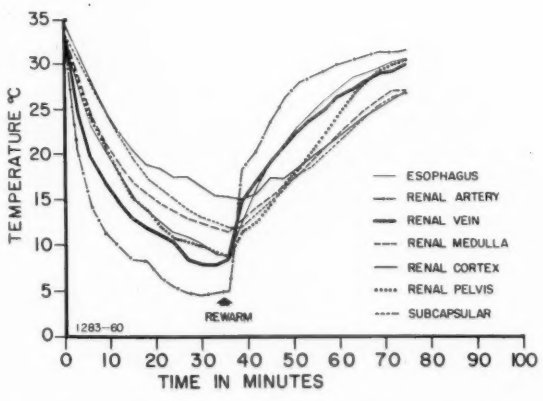

Fig. 5. Temperatures recorded from different parts of the kidney.

thermia results in marked temperature gradients throughout the body during the periods of both cooling and rewarming. This variation not only exists from organ to organ, but is observed when temperatures are recorded from different parts of the same structure. Simultaneously recorded temperatures from different parts of the brain, heart, kidney, and liver demonstrate evidence of markedly uneven cooling and rewarming. The lower the temperature, the more pronounced become such gradients. No correlation could be established between such thermal differentials in the heart and the onset of ventricular fibrillation encountered in hypothermia. The relation of these findings to oxygen consumption is commented upon, and it is concluded that if protracted circulatory arrest is to be contemplated with profound hypothermia, effort must be made to obtain more uniform cooling.

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Percutaneous iliofemoral arteriography

ROBERT A. SCHOBINGER, M.D.
BRONX, N. Y.
From the Bronx Veterans Administration Hospital and Department of Surgery, Albert Einstein College of Medicine

Angiography has contributed greatly to the better understanding, and thus to the therapy, of arterial and venous disease states. The accelerated interest in diagnosis and therapy of arterial insufficiency represents one typical example of the increased activity in this challenging and important field of human pathology. It is well established that adequate surgical therapy for peripheral occlusive arterial disease depends upon the objective evidence provided by properly executed arteriograms. Increasing experience has demonstrated that occlusive arterial disease in the leg may be associated with definite, yet asymptomatic, arteriosclerotic changes within the abdomen.[4, 12] These alterations may be diffuse or segmental and of variable degrees. Such changes affecting the arterial system above Poupart's ligament may sooner or later progress to complete obstruction of the arterial lumen and jeopardize the success of well-performed peripheral arterial operations. Arterial disease cephalad to the femoral canal is frequently not suspected and therefore not investigated if both femoral pulses appear to be of equal quality and if the symptomatology points only toward femoropopliteal involvement.

In the presence of unequal femoral pulsations, aortography is usually considered to be the diagnostic method of choice. By aortography is meant the direct translumbar approach and not the intravenous type of aortography, since the latter technique, in my opinion and the opinions of other workers in this field,[6, 8, 11] has yet to demonstrate a reliability similar to that of the time-honored and well-established direct method. Initially we extended the use of aortography to patients who exhibited evidence of peripheral arterial occlusive disease with rather rapid cephalad progression of the morbid process. In such patients aortography rather than femoral arteriography was performed, even if both femoral pulses were of equal quality. In so doing, we occasionally discovered unsuspected involvements of the aortoiliac system which imposed a modification on the original surgical planning.

For the past 18 months we have made an effort to opacify the iliac arteries and distal aorta in the course of percutaneous femoral arteriography. We have found that the introduction of contrast medium at the level of the common femoral artery allowed excellent opacification of the aortoiliac system in surprisingly many cases in addition to permitting the visualization of the more peripheral arterial tree. This was considered to represent a definite advantage over aortography by which the proper evaluation of the arterial outflow tract in the calf was occasionally not possible or often was obtained only with difficulty.

Our present indications for iliofemoral arteriography include peripheral occlusive arterial disease, regardless of the slow or rapid cephalad progression of the arterial disease process. Earlier we performed iliofemoral arteriograms only in patients with bilaterally equal femoral pulses. Now we

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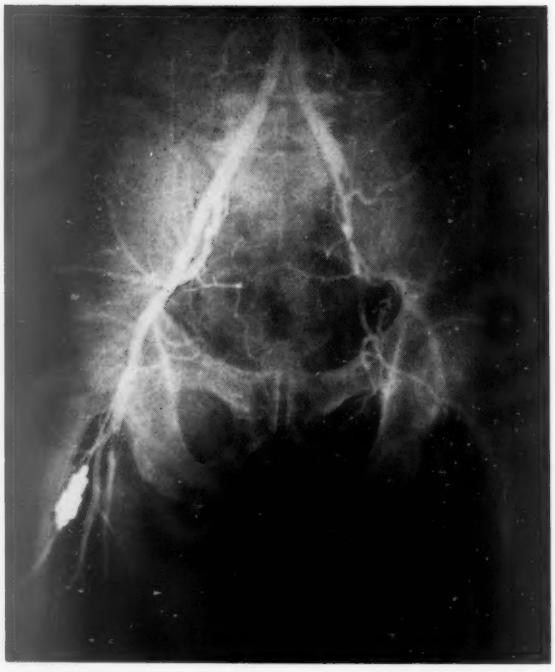

Fig. 1. Right percutaneous iliofemoral arteriogram performed on patient under 2 per cent procaine local anesthesia. Two sets of films. Total amount of contrast medium was 40 ml. Right pedal and left femoral pulses were clinically absent and right popliteal pulse was weak. Arteriogram shows block in right superficial femoral artery and narrowing of popliteal artery. There is absent opacification of the iliofemoral system on the left with replacement by an extensive collateral network, and faint outlining of the distal aorta.

employ this method also in subjects with bilaterally palpable, yet unequal, femoral pulses and whenever possible, even in patients with only one pulsating common femoral artery (Fig. 1). Translumbar aortography can always be resorted to, should, in this last category of patients, the aortoiliac system escape satisfactory opacification by unilateral femoral injections. From this brief exposé can be seen that we have become increasingly selective in our indications for aortography.

RATIONALE

Symptomatic peripheral arterial occlusive disease may, as was already mentioned, coexist with asymptomatic arterial changes at a more proximal level (Figs. 2 and 3). Since the natural history of arteriosclerosis is toward progression, there sooner or later will come the moment of symptomatic proximal arterial insufficiency. From the therapeutic and prognostic points of view it seems important to recognize such latent changes prior to the institution of definitive operation on the major branches of the femoropopliteal axis. The evaluation of the arterial inflow tract may have been unduly neglected in the past in favor of a rather detailed investigation of the various outflow or "runoff" patterns. More attention should be paid to the condition of the arterial tree over some distance proximal to a peripheral arterial occlusion. This precaution may further improve the selection of patients for operation and the type of procedure could also be better adapted to an individual situation. The second point to be emphasized is that the unilaterality of symptoms of arterial occlusive disease does not necessarily correspond to the ipsilaterality of maximal arterial involvement. We have on several occasions seen patients who presented symptoms of ischemia only in 1 leg, but who on arteriography exhibited a comparatively more advanced occlusive process in the opposite asymptomatic lower extremity. Such observations were mainly made because of our insistence to routinely obtain arteriograms of

both lower extremities at the same sitting, even if only 1 leg appeared involved.

PRINCIPLE

The procedure consisted usually of simultaneous bilateral percutaneous femoral arteriography with retrograde opacification of the iliac arteries and distal aorta. Obviously, when only 1 femoral pulse is palpable, the procedure is restricted to that side. Two purposes are thus fulfilled. First, the proximal arterial system can be evaluated in conjunction with that of the leg and, second, both femoral arteries and their branches are outlined simultaneously for valuable comparative studies. In other words, an attempt is made to roentgenographically evaluate the arterial inflow and outflow tracts of both lower extremities by a rather simple and safe method, an attempt which in the vast majority of instances is successful. Similar thinking led Sammons and Mahin[9] to employ retrograde aortography and pelvic arteriography. These workers apparently resort only to a unilateral percutaneous femoral puncture and apply a tourniquet distal to the site of injection in order to favor the retrograde diffusion of contrast medium within the iliac arteries, aorta, and opposite femoropopliteal system. The principle of this technique is not new. It is in this respect worth while to recall the pioneering work of Castellanos and Pereiras[1, 2] and the stimulating contributions of Fariñas,[5] Peirce,[7] and Seldinger.[10] In contradistinction to the customary practice of applying a tourniquet distal to the site of injection in order to facilitate the countercurrent diffusion of contrast material, we prefer not to subject an already diseased artery and extremity to the additional insult of external constriction. A partial or total arterial occlusion below the common femoral artery acts as an obturator of sufficient im-

Fig. 2. Right percutaneous iliofemoral arteriogram. Spinal anesthesia was used. Total amount of contrast medium was 40 ml. Composite picture combines the abdominal phase of the first set of films with the femoropopliteal pattern of the second set exposed 6 seconds later. There were clinically absent pulses on the right below a strongly pulsating common femoral artery. Left lumbar sympathectomy had been performed previously. Arteriogram shows marked sclerosis of distal aorta and right common iliac artery, complete obstruction of right superficial femoral artery from its origin down, high origin of right anterior tibial artery, and diffuse sclerotic changes of left superficial femoral artery with poor popliteal outflow tract.

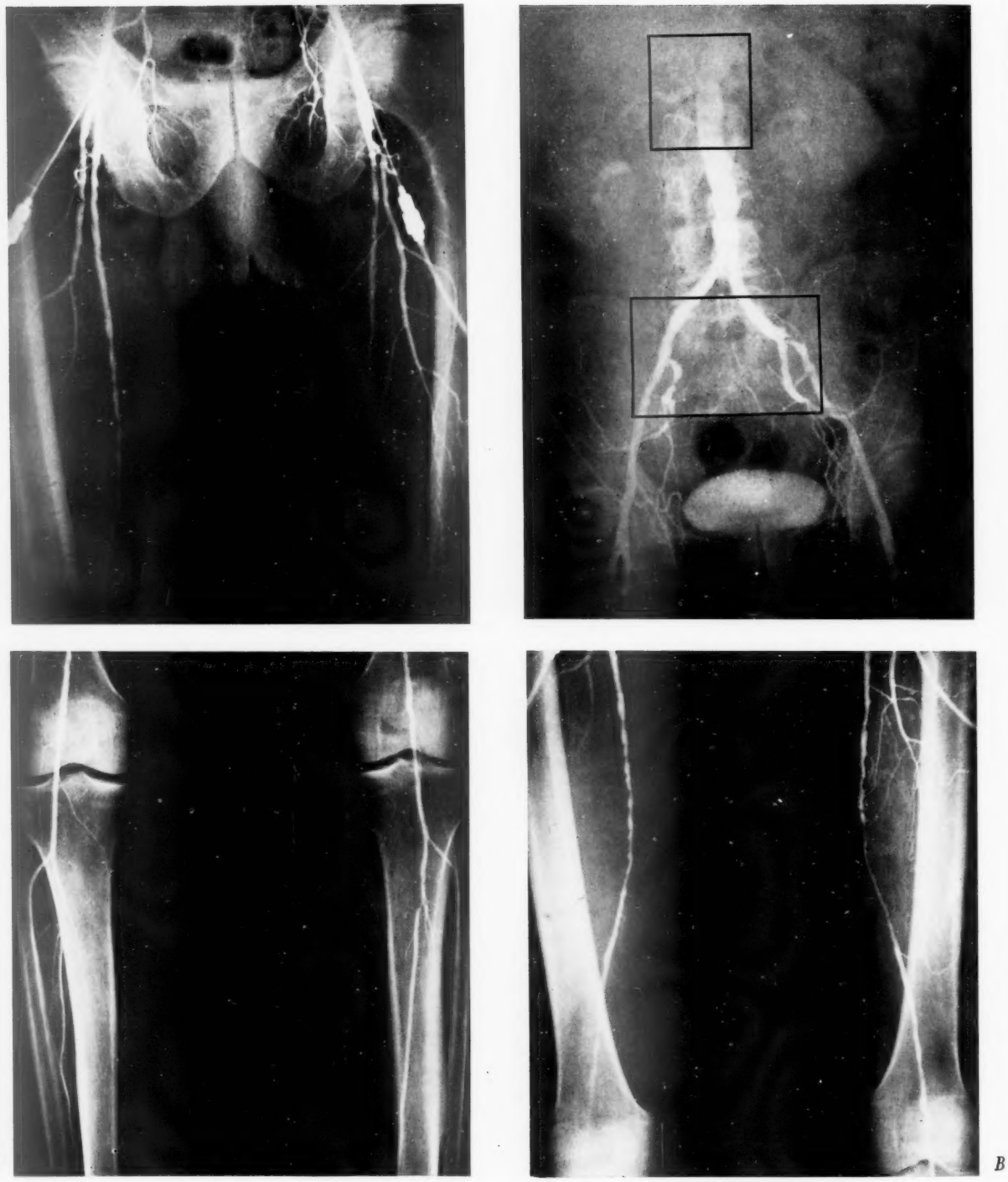

Fig. 3. *A,* Bilateral percutaneous femoropopliteal arteriogram. Spinal anesthesia was used and 30 ml. of contrast medium was simultaneously injected into each artery. Clinically there were unequal common femoral and popliteal pulses (weaker on left), faint posterior tibial pulse on left, and absent pedal pulses on right. The picture is composite. Diffuse sclerotic changes of the superficial femoral arteries are demonstrated, particularly on the right, with bilaterally narrowed popliteal outflow tracts. *B,* Bilateral ileofemoral arteriogram of same patient. Simultaneous, forceful injection of 40 ml. of medium into each artery was used. This is the first set of films. The aorta is opacified to slightly above the renal vessels. Arteriogram shows sclerotic changes of entire visualized portion of abdominal aorta, iliac vessels, and both superficial femoral arteries. Note unsuspected sclerotic changes in aorta and right renal artery (upper box), and narrowing of right internal and left external iliac arteries (lower box).

portance to permit satisfactory retrograde opacification of the aortoiliac system without the aid of external measures.

ANESTHESIA

Iliofemoral arteriography can satisfactorily be performed on a patient under local, spinal, or general anesthesia. We have employed all 3 modalities, but have adopted spinal anesthesia as the method of choice whenever possible since it is usually well accepted by the patient, can be carried out readily in the x-ray room, and provides maximal vasodilatation. If local anesthesia is to be used, it is important to adequately sedate the patient with Demerol (100 mg.) and Seconal (100 mg.) administered 1 hour prior to the procedure. A solution of 2 per cent procaine is employed, 3 to 4 ml. of which is injected directly into the artery 1 to 2 minutes prior to the injection of contrast medium. The introduction of procaine usually produces a sensation of warmth and occasionally of burning, the appearance of which at the various levels in the leg is a precious guide for the proper timing of the roentgenographic exposures. We did not observe any immediate or late ill effects after the intra-arterial injection of 2 per cent procaine, and the arteriographic details have, in our hands at least, been highly satisfactory (Fig. 1).

TECHNIQUE

In view of the increased interest in peripheral vascular diseases, many institutions have developed their own type of roentgenographic device for single or multiple exposures. Seriography is almost always required for the adequate capture of the vascular pattern distal to a complete occlusion. This is frequently accomplished exposure to 2 series of films at 3 to 5 second intervals. Whatever device is employed, the large-size films should be used to make adequate aortofemoral or femoropopliteal arteriograms. In our institution we employ two 14 by 17 inch films contained in grid cassettes in lengthwise juxtaposition in a film tunnel to allow the exposure of 2 sets of films at any desired interval. This arrangement normally encompasses the entire lower extremity or the aorta from the level of the renal arteries to the trifurcation of the popliteal artery (Fig. 3, *A*).

Comfortable positioning of the patient can easily be achieved by placing a long piece of foam rubber, sandwiched between 2 folded bed sheets, on top of the roentgenographic device. This arrangement, furthermore, will allow the effortless modification of the patient's position by simply pulling in the desired direction on the lower sheet.

For femoropopliteal arteriography the patient is positioned in such a manner as to include in the proximal film both anterior superior iliac spines. This positioning allows the capture of the arterial system of the leg from slightly above Poupart's ligament to a point slightly above the ankles (Fig. 3, *B*). It is advisable to rotate the legs of the patient internally by spreading the heels and taping the overlapping toes together. This internal rotation opens the interosseous space roentgenographically and allows a much better identification of the various branches of the popliteal artery. Preliminary scout films are always obtained to verify the correct positioning of the patient and the various roentgenographic factors. The latter are, for femoropopliteal arteriography, 300 Ma., 75 to 80 KVP, one-fourth second. For aortofemoral arteriography, the factors are 300 Ma., 85 to 90 KVP, one-fourth second. The beam is filtered by 2 mm. of aluminum. In order to compensate for the difference in density between the abdomen and the thighs or the thighs and the calves, respectively, a sheet of black paper is placed over the distal film at the time of the loading of the cassette. We found that this method is more easily remembered by the x-ray technician than the change from a conventional to a tapered filter. The focus–film distance is 5 feet in both instances.

For iliofemoral arteriography the patient's position is modified to situate the upper edge of the film at the level of the xiphoid process.

Principles of strict asepsis must be fol-

lowed during the entire procedure. The person performing the injection should wear cap and mask. Both inguinal areas, which should have been shaved, are widely disinfected with 3 layers of tincture of Merthiolate which is prevented from running down along the genitals by properly placed sponges. Then the groins are suitably outlined by sterile towels. A 17 gauge spinal needle with a long bevel is employed for arterial cannulation. The site of puncture is ideally situated 1 fingerbreadth below Poupart's ligament. For a right handed person standing on the right of the patient, the artery is palpated with the middle finger and index finger of the left hand, which are slightly spread. The needle, with stylet in place and at a 45 degree angle with its tip aimed cephalad, is introduced between these 2 fingers. Once the needle reaches the femoral sheath, transmitted pulsations may be felt. Further advancement of the needle will, as a rule, lead to compression of the arterial lumen. At this moment the pulsations above the needle will usually persist, though diminished in intensity, and can still be felt by the middle finger, while they are obliterated by the needle in a distal direction and escape palpation by the index finger. Further advancement of the needle will place its tip into the arterial lumen. The stylet is gently withdrawn and if the needle is properly placed a jet of arterial blood accompanied by rhythmical motions of the needle is observed. Should no arterial blood flow from the needle upon removal of the stylet, it is best to slowly withdraw the open needle with a rotary motion. Often both walls of the artery have been traversed and slight withdrawal of the needle will place its tip correctly within the lumen of the artery. The absence of a free flow of blood accompanied by a rhythmical motion of the needle in a

Fig. 4. Right percutaneous iliofemoral arteriogram. Spinal anesthesia was used. Total amount of medium was 30 ml. There were clinically absent pulses at all levels in the left lower extremity and a strongly pulsating common femoral artery with weak popliteal and pedal pulses on the right. Picture is composite, and the second set of films was exposed 8 seconds after the first. Arteriogram shows block of left external iliac artery bridged by collaterals and segmental narrowing of origin of right superficial femoral artery. Both superficial femoral and popliteal arteries are somewhat narrowed, including the outflow tracts in the calves.

horizontal plane, or a slow flow of dark blood, indicates that the needle had been placed laterally to the artery. The detail of bidigital palpation of the artery shortens the time required for arterial cannulation and eliminates blind poking or traumatic "fishing" for the vessel. The introduction of the needle with sylet in place prevents obliteration of its lumen by fragments of soft tissues or calcified material. Once the needle is properly placed it is, without stylet, gently advanced about 2 cm. in a cephalad direction so as to place its tip within the lumen of the external iliac artery. The stylet is then replaced and the opposite common femoral artery cannulated in a similar fashion if bilateral arteriograms can be performed. The plastic tubings which previously had been filled with sterile normal saline solution and to which a 2-way stopcock had been applied on the syringe side, are now connected to the needles. Each tube is immediately flushed clear of all blood with saline solution and the stopcock closed while the solution is being injected. This will replace the metallic stylet with a physiologic obturator consisting of incompressible liquid. From this moment on the needle is no longer manipulated. All the handling is done at the other end of the plastic tubing in order to minimize the danger of dislocation or contamination of the needle. Superimposition of the plastic tubing on the femoral artery can be avoided by deflection of the tubing laterally. If the examination is carried out under local anesthesia we customarily inject 3 to 4 ml. of 2 per cent procaine into each artery just prior to the connection of the tubings to the needles. This injection precedes the introduction of contrast medium by 1 to 2 minutes.

Bilateral femoropopliteal arteriograms are obtained by having 2 persons introduce simultaneously and under constant pressure 30 ml. of contrast medium into each artery. The contrast material employed in all our arteriograms consists of a 50 per cent solution of diatrizoate (Hypaque). Synchronization is important and the time required for such a manual injection amounts to approximately 4 seconds. This rate of injection is used to create an adequate bolus of contrast medium. The first set of films is exposed while the last 3 to 4 ml. of medium is injected and the second set 4 to 8 seconds later. The shorter interval is selected when only a moderate degree of ischemia of the extremity exists, when incomplete occlusions are anticipated, or when a careful clinical examination of the extremities has shown a palpable flow through collateral arteries such as the genicular vessels. A 6 to 8 second interval is chosen in the presence of advanced ischemia or of a complete block without palpable collaterial circulation. Immediately after the injection the needles and tubings are thoroughly flushed with saline solution and the stopcock closed. The needles are not withdrawn until the immediately developed films have been inspected and the arteriograms found to yield the desired information.

For iliofemoral arteriograms the patient's positioning is modified in the manner described. Either new syringes are employed or the previously used ones thoroughly flushed with saline solution to prevent clogging. These little details are purposely emphasized because it is amazing how frequently they are forgotten! Each syringe is filled with 40 ml. of contrast medium which this time is forcefully injected, again simultaneously by 2 persons. The timing of the roentgenographic exposure corresponds to that mentioned for femoropopliteal arteriography. We thus have obtained retrograde arteriograms encompassing both iliac arteries and the aorta up to and including the renal arteries (Fig. 3, *A* and *B*).

During the period ranging from Jan. 1, 1959, to June 30, 1960, inclusively, we performed bilateral femoral arteriograms on 82 patients. Excellent opacification of both femoropopliteal systems was obtained in 80 patients, while in the remaining 2 patients only the arteries in 1 leg were visualized because of unilateral extravasation of contrast medium. The iliac vessels and distal aorta were outlined to a degree satisfactory for diagnosis in 71 patients. The reasons for

inadequate aortoiliac angiograms in 6 patients were unilateral extravasation (2), motion (2), and faulty timing of the roentgenographic exposure (2) Adverse reactions to the contrast medium after the first injections rendered repeat injections inadvisable in 2, and in 3 patients no attempt at retrograde opacification of the aortoiliac system was made. Unilateral femoral punctures with counter-current opacification of the iliac arteries, aortic bifurcation, and contralateral iliofemoropopliteal system was performed in 10 additional patients, bringing the total of patients included in this study to 92. The latter examination was successful in 9 instances. In the remaining patient the contralateral femoropopliteal arterial tree could not be visualized adequately because of its involvement by extensive occlusive disease.

SUMMARY

The described technique allows the opacification of the arterial inflow and outflow tracts in arterial occlusive disease of the lower extremities as well as a simultaneous comparative angiographic study of the arterial system of each leg.

The angiographic data collected in the course of such examinations have confirmed the presence of diffuse and/or segmental arterial occlusive disease at levels usually not encompassed by conventional peripheral femoral arteriography.

It can be anticipated that such extended and well-tolerated angiographic studies will shed more light on the over-all process of arteriosclerosis. They will also invite additional improvements in the selection of patients for direct arterial operations. The more adequate evaluation of the hitherto somewhat neglected inflow tract may influence the planning of therapeusis. The discussed method of bilateral simultaneous opacification of the entire arterial system of both lower extremities provides also a unique opportunity to study the vascular status of an asymptomatic leg, the counterpart of which is affected by symptomatic occlusive arterial disease. Thus, improved diagnostic insight may lead to a better therapeutic approach and even have prognostic implications.

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A new operation for transposition of the great vessels

HARRIS B. SHUMACKER, JR., M.D.
INDIANAPOLIS, IND.
From the Department of Surgery and Research Center, Indiana University School of Medicine

Up to the present time, transposition of the great vessels has been treated primarily by various palliative procedures designed to increase the admixture of venous and arterialized blood either by creation of an atrial septal defect or by partial venous retransposition.[2, 3, 5] Since Albert's[1] suggestion that complete correction might be accomplished by intra-atrial retransposition, several additional operations aimed at this end[4, 6, 7] have been proposed. This report describes another method by which this can be achieved. That it effectively shunts vena caval and coronary sinus blood into the posterior ventricle through the mitral valve and pulmonary venous return into the anterior ventricle through the tricuspid valve is evident from animal experiments and 2 clinical cases.

OPERATIVE PROCEDURE

An incision is made in the right atrial wall close to and parallel to the interatrial groove (Fig. 1). Another longer curved incision is made toward the left side of the right atrium, beginning near the left side of the inferior vena cava and ending near the left side of the superior vena cava. Through this incision the right atrial cavity is inspected and the atrial septum is excised as completely as possible. The right side of the atrial flap is sutured to the right lateral margins of the venae cavae, the right lateral margins of the septal ring, and the left atrial wall to the left of the points of entry into the left atrium of the pulmonary veins. The left side of the flap is then sutured to the left lateral margins of the posterior caudal wall of the right atrium, beginning at the left side of the inferior vena caval orifice and extending in a cephalad direction to the left of the coronary sinus, the cut edge of the base of the septum, and across the remaining cephalad posterior aspect of the right atrial wall up to the left lateral margin of the superior vena cava. The vena caval and coronary sinus flow has now been diverted into the posterior ventricle. The procedure is completed by suturing an oval graft to the right and left edges of the free right atrial incisions and the presenting anterior surfaces of the superior and inferior venae cavae. This shunts the pulmonary venous drainage around and over the previously constructed tunnel into the anterior ventricle via the tricuspid valve.

The same objective can be gained with a modification (Fig. 2). The original incision through the right side of the right atrial wall is made a little farther to the left of the interatrial groove. After the second incision is made and a somewhat narrower double-pedicled flap created, an oval patch of Teflon felt or other suitable material is sutured to the right edge of the flap. This graft is then similarly approximated to the left atrial wall to the left of the points of entry of the pulmonary veins. The left edge of the flap is sutured in place as previously described. The remaining free edges of the

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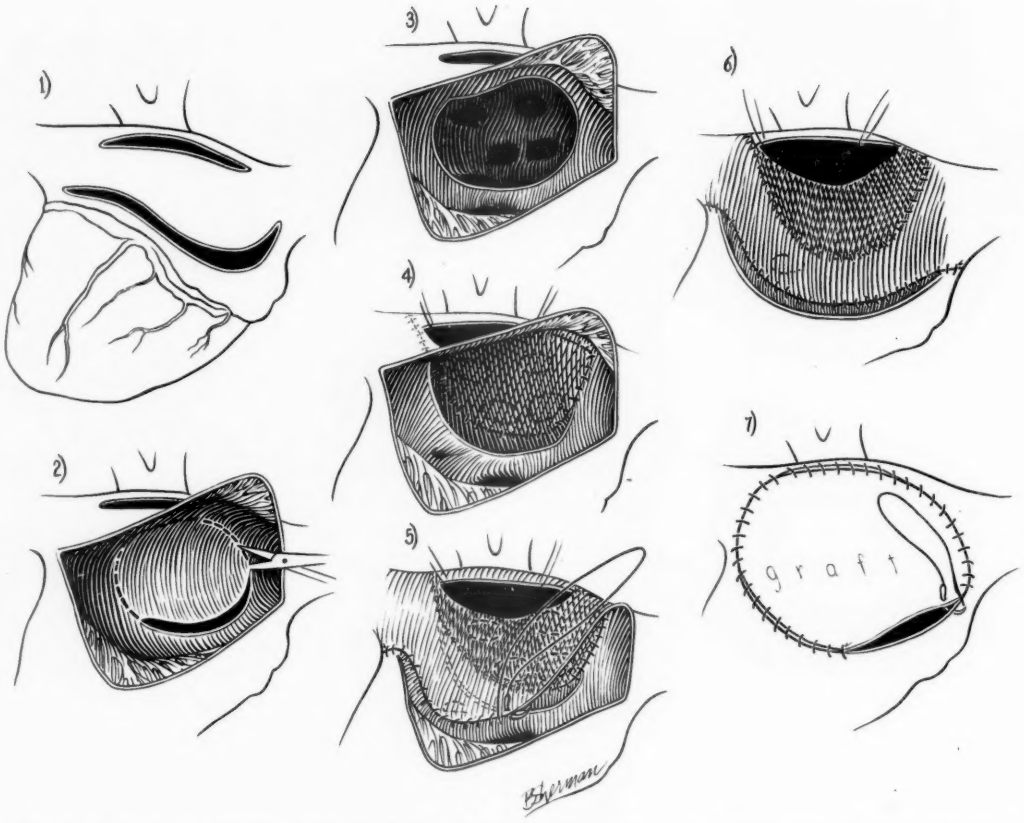

Fig. 1. Drawings which illustrate intra-atrial retransposition. *1,* The right atrial incisions; *2,* excision of atrial septum; *3,* view of pulmonary veins and portion of mitral orifice; and *4,* suture of right side of atrial flap to the right of the mitral orifice. For clarity of illustration, length of the line of suture is exaggerated and represents the point of attachment to the left atrial wall. Actually, since the side of the right atrial flap is shorter, the left atrial wall is "tented up" or "purse-stringed" in a fashion as the suture is accomplished. *5* and *6,* Suture of left side of right atrial flap to atrial wall. The vena cava–coronary sinus tunnel is now complete. *7,* Reconstruction of anterior atrial wall by means of a graft.

right atrium are then directly approximated and sutured above and below to the anterior walls of the superior and inferior venae cavae.

In experimental animals, the completeness of the transposition is evident from roentgenographic studies with contrast material. When contrast material is injected into a pulmonary vein, the right ventricle and the pulmonary arterial tree become opacified. When the injection is made into a vena cava, the vena caval tunnel and the coronary sinus are opacified, as well as the left ventricle, the coronary arteries, and the aorta.

CASE REPORTS

Case 1. The patient was a very ill 10½-month-old male infant who had had cyanosis since birth, progressive respiratory difficulty, and poor weight gain. He weighed only 8 pounds, 13 ounces, at the time of operation. He was admitted to the hospital on Sept. 5, 1960. Catheterization and cineangiographic studies through the saphenous vein and by percutaneous ventricular puncture established the diagnosis of transposition with bidirectional shunt through an atrial septal defect. Pressures were 101/11 mm. Hg in the right ventricle, 113/64 in the aorta, 2.4 in the right atrium, and 5.4 in the left atrium. The femoral blood was 48.7 per cent saturated and rose only to 53.6 per cent saturation during oxygen inhalation. The patient was treated for diarrhea and with digitalis and diuretics for heart failure. Though the lungs remained relatively free of râles and the liver was not remarkably enlarged, peripheral edema became progressively more marked while the infant was in the hospital in spite of intensive treatment. He remained listless and cyanotic.

Operation was carried out on September 30.

The infant seemed nearly moribund at the time. Arterial pressure could not be obtained by sphygmomanometric means and as soon as the radial artery was catheterized for this purpose shortly after induction of anesthesia, the systolic pressure was only 20 mm. Hg. It improved, however, after the administration of vasopressors. The left iliac vein was catheterized through the left saphenous vein for intravenous administration of fluids. The inferior vena cava was catheterized through the right common iliac vein exposed through a right lower quadrant extraperitoneal incision. At the same time, the arterial cannula was introduced into the right iliac artery. A right anterolateral thoracotomy incision was made. The tissues at the site of each incision were markedly edematous. There was free pleural fluid and marked increase in the amount of pericardial fluid. It had been hoped that it would be possible to catheterize the superior vena cava via the azygos vein but the latter was too small to permit introduction of a catheter of adequate size. Consequently, the superior vena cava was catheterized directly through its anterior wall. Inflow and outflow catheters were connected with a rotating disc oxygenator, partial bypass was begun, and the patient was cooled to a rectal temperature of 26.7° C. The venae cavae were now occluded and ventricular fibrillation induced by electric shock. The first operative procedure described was then carried out without significant difficulty. On exploration of the atrium, a secundum type defect approximately 1 cm. in diameter was found. The septum was excised. The vena cava–coronary sinus tunnel was created with the double-pedicled right atrial flap and the anterior atrial wall was reconstructed with a patch of woven Teflon. Warming was begun. When the temperature had risen to 29° C. ventricular fibrillation ceased spontaneously with return of good ventricular contractions. The color of the patient improved remarkably. When the extracorporeal circulation was discontinued, the heart action remained quite good for a while. Unfortunately, the operative procedure was now necessarily prolonged because of difficulty in securing hemostasis, particularly from the sutured iliac vessels. There was also some lesser difficulty in securing hemostasis along the edges where the patch had been sutured to the atrial wall and venae cavae. During this period, the blood pressure dropped to approximately 60 mm. Hg systolic. The wounds were closed and the patient returned to the recovery room. The color remained good but the pressure continued at about the level of 50 or 60 mm. Hg in spite of blood replacement and the use of vasopressors. About 4:00 P.M. the child died. Postmortem examination showed no other congenital defects and the retransposition seemed to have been adequately performed.

Case 2. The second patient was a 2-day-old infant who was admitted on Oct. 12, 1960. He had been cyanotic and, in spite of oxygen administration, had had rapid and difficult respiration since birth. He was found to be cyanotic and had fast irregular breathing, hepatomegaly, and peripheral edema. Cardiac catheterization and cineangiography performed on Oct. 24 showed evidence of transposition of the great vessels, a ventricular septal defect with bidirectional shunt, a patent foramen ovale, and a patent ductus arteriosus. The aortic blood was only 67.5 per cent saturated while the infant was breathing oxygen. In spite of diuretics and digitalization, the peripheral edema increased.

At the time of operation on November 16, the infant weighed only 9 pounds, 6 ounces. No blood pressure could be obtained when he was brought to the operating room, though it was 50 mm. Hg systolic when the internal mammary artery was later catheterized. The inferior vena cava was cannulated via the left common iliac vein and later the superior vena cava was cannulated through the azygos vein. The arterial inflow cannula was placed in the external iliac artery. A bilateral thoracotomy incision was made. All the tissues were markedly edematous. The patent ductus arteriosus was isolated and ligated when partial bypass was begun. The patient was cooled to 25° C. rectal temperature. The heart went into standstill as this low temperature was reached. The atrial retransposition was accomplished without difficulty according to the modified procedure previously described. A small segment of Dacron graft was sutured to the right side of the atrial flap and after the vena cava–coronary sinus tunnel had been created, the anterior atrial wall was closed directly and sutured across either end to the anterior surfaces of the superior and inferior venae cavae. The ventricular septal defect was repaired through a ventriculotomy incision.

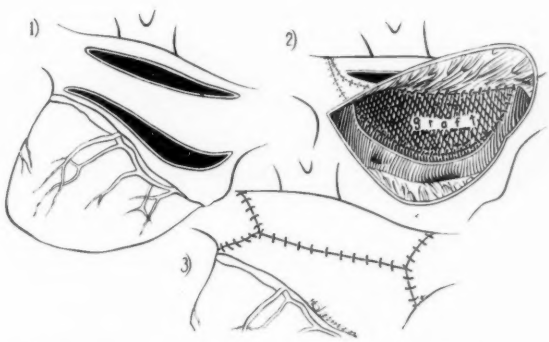

Fig. 2. Drawings which illustrate modified procedure. *1*, The atrial flap is created; *2*, the graft is sutured to right side of flap and to left atrial wall; and *3*, the procedure is completed.

Unfortunately, the venous outflow catheters were so small that it was impossible to use an adequate perfusion rate. Indeed, at one time the rate had to be reduced to 180 ml. per meter squared. In spite of this poor perfusion, the blood pressure ranged between 40 and 50 mm. Hg systolic throughout the procedure. It was possible to cool the infant fairly rapidly, but because of the poor flow rate it took an inordinately long time to rewarm him. Though the repair was completed within approximately 1 hour, it was nearly 3 hours before the patient was adequately rewarmed. As the patient became warm, the heart went into ventricular fibrillation. This was corrected with electric shock. Because of the poor perfusion during rewarming, cardiac massage was also carried out. A blood pressure ranging between 40 and 70 mm. Hg was thus maintained. When the extracorporeal circulation was discontinued when the infant's temperature was 35° C., the blood pressure was approximately 40/20, the heart was seemingly contracting well, and the patient's color was good. During closure of the anterior chest wall, however, cardiac arrest occurred and it was impossible to bring about resuscitation.

Operation in both cases was undertaken as a desperate measure with the realization that there was relatively little chance of success. Both infants were in very poor condition and in marked heart failure. One weighed less than 9 pounds and the other only 9 pounds, 6 ounces. Disappointing as the outcome was, there were some gratifying aspects. It was satisfying to know that the procedure could be accomplished in such tiny infants. After repair, both had a period of apparently good color and reasonably good heart action. In both cases, difficulties arose which should be averted in future attempts. In the first, the operation was unduly prolonged by difficulty in securing hemostasis, particularly from the repair of the iliac vessels. In the second, it was greatly prolonged because of the small caliber of the venous drainage tubes and the consequent poor perfusion rate.

DISCUSSION

The operation described consists essentially in the diversion of vena caval and coronary sinus blood flow into the posterior ventricles by creation of a tunnel constructed by means of a double-pedicled right atrial flap and reconstruction of the anterior right atrial wall so as to permit pulmonary venous blood to flow through the tricuspid valve into the anterior ventricle. The first alternative method outlined works well in the dog and was accomplished without difficulty in the first clinical case. Though there is considerable disparity between the length of the right side of the atrial flap and the distance between the points of caval-atrial junction around the left atrium to the left of the points of entry of the pulmonary veins, this seems to present no real difficulty. Sutures are simply placed more closely on the flap than on the left atrial wall. It appears likely that its use in all patients except those with massive right atrial enlargement would necessitate reconstruction of the right anterior atrial wall by means of a graft rather than by direct suture. I believe that it would be better to utilize a pericardial graft covered with thin Teflon felt since this might permit an easier blood-tight closure.

The second modification was easily carried out in the second case. Adding a plastic extension of an appropriate size and shape to the right side of the atrial flap permits a narrower atrial flap, and it is likely that reconstruction of the anterior wall of the right atrium could be accomplished fairly regularly by direct-suture closure.

The first is probably the better method since one can make the anterior atrium as large as he wishes and thus can be assured of adequate room around the vena cava–coronary sinus tunnel for free flow of blood from pulmonary veins through the tricuspid valve. It appears to have certain potential advantages over previously described methods. The use of the atrial septum itself as described by Albert is unlikely to prove suitable for human beings in view of the small size of the septum and the frequency with which the amount of available septal tissue is still further decreased because of the presence of an atrial septal defect. The creation of the interatrial tunnel exclusively by means of a prosthesis, as suggested by Merendino and his associates[6] and by Creech and his colleagues,[4] appears unwise since it would not grow with increasing size of the patient and the heart. With either of the 2 procedures I have described, the grafts used constitute only a portion of the repair

and viable autogenous tissue makes up the rest. Hence, there should be no difficulty with growth. The multiple-flap method of Senning[7] has to commend it the incontrovertible fact that it is, as far as I know, the only method yet successfully applied in human beings. The proposed procedures seem to be simpler in execution.

Just what approach would prove best remains to be seen. In the first clinical case, a right anterior thoracotomy incision was quite satisfactory. In this instance, there was no additional anomaly except for the atrial septal defect. In the second, in which a patent ductus arteriosus was present, a bilateral anterior thoracotomy incision worked well. If a ventricular septal defect were present and there were no patent ductus arteriosus, perhaps a sternum-splitting incision would be better. This matter could be settled by further clinical trials.

The difficulty encountered in the first case in securing hemostasis should be obviated by use of a pericardial graft, perhaps best also covered with thin Teflon felt, for reconstruction of the anterior atrial wall and use of the proximal end of the right subclavian artery for the arterial inflow catheter. I have subsequently found that the right subclavian artery can be adequately mobilized even through a sternum-splitting incision to permit introduction of the inflow catheter through its proximal end into the aorta. The subclavian artery can then be ligated at the completion of the procedure, eliminating the necessity for arteriorrhaphy on such a tiny vessel. When the iliac vein is exceedingly small as was true in this case, it could be safely ligated rather than repaired. The inadequate venous outflow in the second case presented a more difficult problem but a solution seems to be at hand. At the moment, it is my feeling that if a similar situation is encountered I should place the outflow catheters initially in the inferior vena cava via the common iliac vein and in the superior vena cava via the azygos vein. Before beginning perfusion, however, I would introduce a large catheter into the right atrium at a point where the atriotomy could subsequently be incorporated in one of the incisions made to create the atrial flap. This catheter would then be used during the cooling phase for venous outflow and should permit adequate perfusion. Once a low body temperature had been reached, the smaller catheters placed into the superior and inferior venae cavae could be used instead to maintain some extracorporeal circulation during the period of interatrial retransposition. When the corrective procedure had been accomplished, quick rewarming should be possible by draining off venous blood through a fairly large catheter placed through the posterior ventricle into the pulmonary artery.

SUMMARY

A new method for interatrial venous retransposition has been described. It seems applicable to cases of transposition of the great vessels.

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Resection of inferior vena cava and graft replacement (aortic homograft) for retroperitoneal sarcoma

CHARLES J. McPEAK, M.D.
NEW YORK, N. Y.
From Memorial Hospital

This report concerns the removal of a right retroperitoneal sarcoma with the resection of the right kidney, along with 13.5 cm. of the infrahepatic portion of the vena cava including the distal 1.5 cm. of the left renal vein. The resected portion of the vena cava was replaced by a segment of preserved homologous abdominal aorta. The divided end of the left renal vein was anastomosed to an opening made in the side of the preserved graft.

CASE REPORT

In 1948, at the age of 50, a woman had begun to experience a dull, rather severe, deep epigastric pain. It occurred predominantly on the right side and penetrated through to the patient's back. Because of persistent pain, and after complete but nonrevealing clinical and laboratory studies, the patient underwent an exploratory laparotomy, at which time no intra-abdominal disease was found. In September, 1952, after a similar nonrevealing survey, the patient underwent a second exploratory laparotomy. At this time, there was a firm mass in the right retroperitoneal area thought to be carcinoma of the pancreas; no resection was attempted. In January, 1953, an exploratory laparotomy was performed and the previously described retroperitoneal tumor mass confirmed. An attempt to remove this retroperitoneal tumor showed that the mass could not be dissected away from the vena cava.

After this operation, the woman was given a course of radiation therapy, the factors of which are unavailable. She experienced transient relief after this treatment, but the pain soon recurred and became increasingly severe. She was admitted to Memorial Hospital where she was given a calculated tumor dose of 3,000 r to the area of the mass through a 10 by 10 cm. anterior portal by the cobalt therapy machine. For nearly 2 months after this treatment there was marked, but again transient, relief of symptoms.

The patient was readmitted to Memorial Hospital in October, 1955. She described the same severe, dull, persistent pain in the right upper abdominal quadrant with penetration straight through to the back. Examination showed her to be a pale, lean woman who evidenced chronic weight loss. In the right upper abdominal quadrant there was a poorly defined mass which did not move on respiration or on bimanual manipulation. There was no evidence of metastases by clinical or laboratory determinations. The inferior vena cava was outlined by injection of Urokon into the left femoral vein through a polyethylene catheter (Fig. 1). This study demonstrated the

Fig. 1. Venogram (Urokon) which shows displacement and partial rotation of the vena cava by retroperitoneal tumor.

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vena cava to have a maximum point of displacement 2½ inches to the right of its normal course. The displacement curve began inferiorly at L_3 and extended up to the level of D_{11}. In addition to the lateral displacement, there appeared to be flattening and longitudinal rotation of the vein by the tumor mass. Intravenous pyelogram showed an indistinct mass in the right renal area, but the kidney itself could not be outlined and there was no evidence of dye excretion from the right kidney. The left kidney was normal in position, outline, and function.

After correction of a deficit in the blood volume, the patient was prepared for operation. Exposure of the operative area was obtained through a transverse epigastric incision. Later, as it became necessary to mobilize the liver superiorly, a right thoracotomy incision was made to divide the diaphragm.

There were diffuse adhesions throughout all the planes of the upper abdomen which resulted from the 4 previous operations as well as the 2 courses of radiation therapy. The pancreas, duodenum, and portal structures were identified and reflected to the left and superiorly. It was then apparent that the tumor was rather discrete and lay posteromedially to the right kidney, posteriorly and more to the left of the vena cava, but anteriorly and to the right of the aorta (Fig. 2). Although this rather firm tumor lay directly over a segment of the aorta and both renal arteries, it was possible to free them of the tumor by dissection in the subadventitial plane of these arterial structures. Such dissection was not possible with the corresponding veins, however, for the vena cava and right renal vein were inseparable from the tumor.

The removal of the tumor mass with the adjacent invaded tissues required the resection of the right kidney, right adrenal gland, and the involved segment of the vena cava. The vena cava segment measured 13.5 cm. in length. In order to provide a free cuff of vena cava superiorly, it was necessary to dissect the vessel free from the inferior 1.5 cm. of the liver. This required the division of the two lowermost hepatic veins. It was found that the left renal vein could be divided between the ovarian vein and the vena cava. A homograft of an abdominal aorta measuring 13.5 cm. in length, which had been prepared by the freeze-dry method, was sutured in place.

In order to anastomose the divided end of the remaining renal vein to the graft without tension, a left nephropexy was performed to support the kidney in a more medial and anterior position. An ellipse was excised from the wall of the homograft to correspond to the size of the left renal vein. The end of the vein was then anastomosed to the side of the homograft with the same type

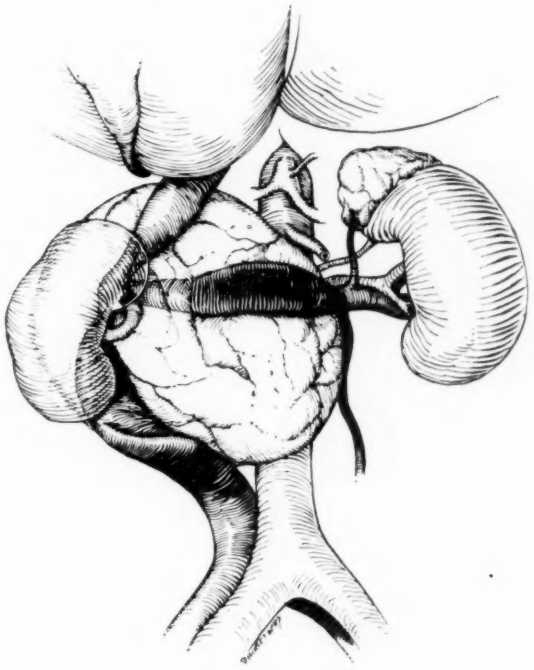

Fig. 2. Sketch which shows the anatomic relationship and position of the tumor.

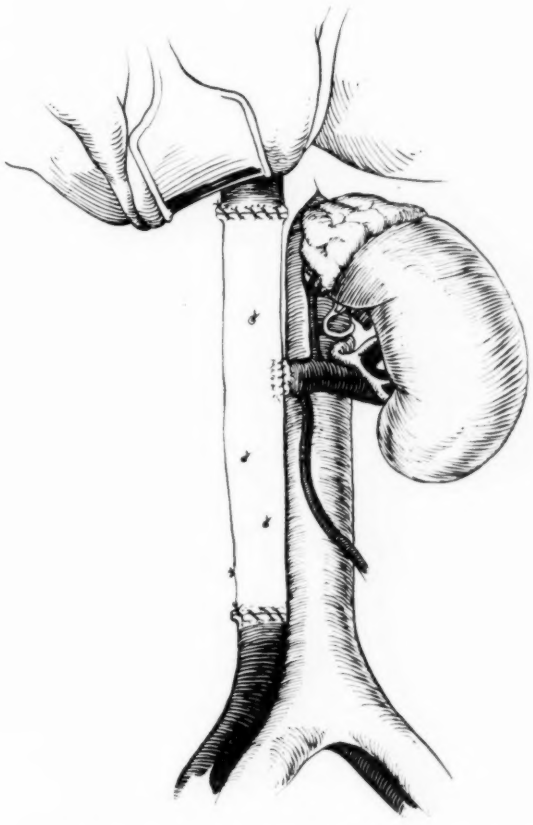

Fig. 3. Drawing illustrates the blood vessel anastomoses with the graft (aortic hemograft) in place.

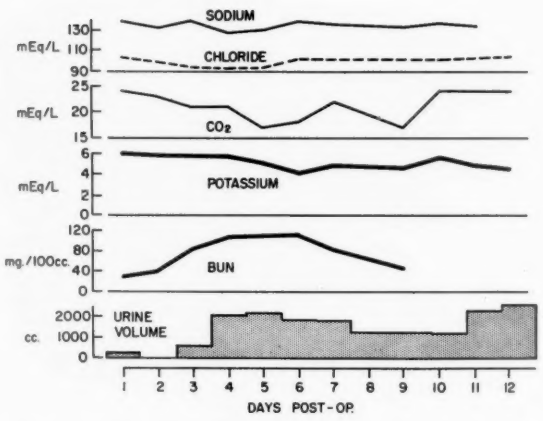

Fig. 4. Graph shows function of left kidney (with renal vein–vena cava anastomosis) as reflected by daily urinary output and simultaneous blood chemistry studies. The elevated potassium level started to fall almost immediately when the urinary output returned on the fourth postoperative day, whereas the fall in the blood urea nitrogen level did not begin until the sixth postoperative day. Note that the potassium level rose again for a brief period at the time of the massive thrombosis on the tenth day.

Fig. 5. Gross specimen which shows invasion and replacement of wall of vena cava by tumor.

of everting No. 5-0 arterial silk suture (Fig. 3). The anastomotic sites were irrigated freely with dilute heparin solution during the procedure. Air was aspirated from the open vessels and replaced with normal saline solution before blood flow was allowed to resume through the graft.

The chest was closed after an underwater drainage system was in place. Two large Penrose drains were left in the right renal space and allowed to emerge through the right lateral end of the laparotomy wound. The patient received 10 units of blood (5,000 ml.) during the operation.

While the inferior vena cava was temporarily occluded, the blood pressure in the arm dropped to 70 to 80 mm. Hg systolic for 1 hour and 20 minutes. The blood pressure rose to 100 systolic after the vena cava clamps had been removed.

Postoperatively, the patient was given heparin in the fluids which were administered intravenously by a continuous drip through a polyethylene catheter inserted into the common femoral vein by way of the saphenous vein. Approximately 200 mg. of heparin was used daily in this manner.

The patient was doing well when, on the tenth postoperative day, she rather abruptly lapsed into coma associated with a fall in blood pressure to 78/0 and an increased pulse rate to 132 per minute. She responded from this hypotensive state with the rapid administration of 600 ml. of plasma and 1,000 ml. of whole blood. At the same time, she was noted to have increased swelling and mottling of both legs and buttocks, especially on the right. The polyethylene catheter in the femoral vein was obstructed and attempts to replace it were unsuccessful, presumably because of a thrombus in both iliac veins. This thrombophlebitis developed in the presence of Ace elastic bandages on both legs from toes to upper groins, as well as a continuous drip of diluted heparin into the venous system below the anastomosis. The massive thrombophlebitis was treated by bed rest, elevation of both legs, and the application of warm wet towels to both lower extremities.

Two weeks after the onset of the thrombophlebitis, the edema of the buttocks began to subside, followed soon afterward by the edema of the thighs and legs. At the time of discharge, 42 days after operation, there was only minimal edema of both ankles after the patient had been out of bed for several hours.

Fig. 4 illustrates the marked depression in urinary output over the first 3 postoperative days. The blood chemistry levels are correspondingly shown.

Pathology report. The specimen as received had the over-all measurements of 14 by 12 by 6 cm. and included the right kidney, right adrenal gland, a segment of the inferior vena cava, and the retroperitoneal tumor. The portion of vena cava was tortuous, and was distorted by the tumor. The vena cava segment measured 11.0 cm. in

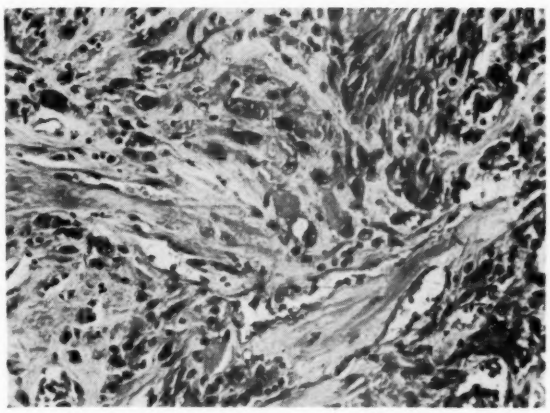

Fig. 6. Photomicrograph of section of tumor which shows both the marked hyalinization and the undifferentiated pleomorphic cellular component of the tumor tissue.

length and showed gross invasion of the wall by the tumor. The tumor mass measured 10.6 by 6.5 by 6.5 cm. It was very firm in consistency, and on sectioning presented a variegated tan to yellow to dark red appearance with a whorled and trabeculated pattern.

The right kidney measured 10.5 by 5 by 3.5 cm. Its capsule was thickened, but it did strip with ease to reveal a smooth cortical surface. The kidney was estimated to weigh 80 grams. On its cut surface the cortex was thin, measuring only 0.3 cm. in dimension. The medullary portion did not appear unusual. The pelvis was slightly dilated, as were the pelvic calyces, but the 2.0 cm. of ureter attached to the renal pelvis was not dilated. The right renal vein showed a normal origin from the vena cava and no obvious site of occlusion (Fig. 5).

Microscopic description. The bulk of the tumor was hyalinized, relatively avascular, and with only scattered, small tumor cells (Fig. 6). The next most common pattern was at the other extreme—an extremely cellular, poorly differentiated, and pleomorphic tumor with many giant cells characteristic of radiation reaction. Inflammation and necrosis were present, but not constant. A few foci were less anaplastic and better differentiated. The sections from the vein wall showed complete replacement of the wall by tumor.

The diagnosis was anaplastic fibrosarcoma with evidence of radiation reaction. The patient had lived without pain in complete comfort and with a full scope of activity for 1 year when pulmonary metastases were discovered. She died shortly thereafter.

A technique of attaching a synthetic graft to the side of a severely arteriosclerotic aorta

JOHN R. DERRICK, M.D.
GALVESTON, TEXAS
From the Department of Surgery, University of Texas, Medical Branch

Currently, bypass grafts are being used with increasing frequency for severe occlusive disease of the major branches that arise from the aorta. The generalized nature of the degenerative process that is known as arteriosclerosis often results in changes in the aorta which mitigate against the successful attachment of a bypass graft. The surgical accessibility of the lower abdominal aorta makes this an ideal region for the attachment of bypass grafts for major abdominal or peripheral arteries; yet, this area is often the most severely involved by arteriosclerosis. The severe degeneration and calcification often leave only a thin layer of fibrous adventitial tissue which does not readily hold sutures, or, if it does, it is found to lack both strength and uniformity.

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A buffer graft around the area affords easy, secure attachment of grafts without the necessity of resection of the severely degenerated portion and extension of the operative procedure. Use of a sheet of woven Teflon around the site, as illustrated in Fig. 1, permits the attachment of a bypass graft. Fig. 2

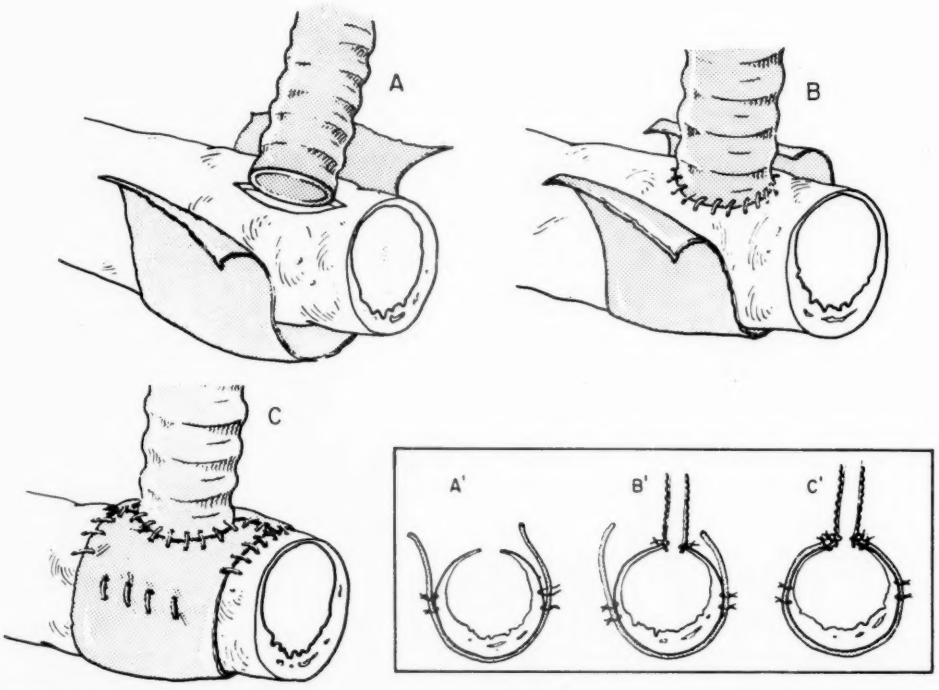

Fig. 1.

Fig. 2.

is a photograph taken at operation of a retrograde flow graft (De Bakey's side-arm graft) which is attached to the lower abdominal aorta and going to the right renal artery.

The graft is initially sutured to the thinned, friable edges of the aortotomy with No. 4-0 arterial silk. The Teflon sheet is then placed around the aorta and trimmed to conform to the graft and the aorta, as illustrated in Fig. 1, *C*. A second row of No. 3-0 arterial sutures, snugly approximating the Teflon sheet to the graft, adds strength and secures the anastomosis. To prevent bleeding and dissection beneath the buffer graft, a running No. 3-0 arterial suture is then made, with use of the adventitial coat of the aorta and the Teflon at a distance of 3 to 10 mm. from the graft anastomosis.

This technique may provide a simple means of graft attachment without the necessity of extensive aortic resections in instances in which the bypass graft attachment is insecure or is not feasible because of severe degenerative changes.

Physiologic evidence of lymphatic repair after skin homotransplantation

R. C. A. WEATHERLEY-WHITE, M.D.*
RICHARD B. STARK, M.D.
MARGIE DE FOREST, A.A.
NEW YORK, N. Y.
From the Surgical Service (Plastic), St. Luke's Hospital in the City of New York

The immunologic nature of the homograft rejection response has been amply documented.[4, 10] Less clear, however, are the means by which this response is initiated.

Evidence at this time points to the regional lymphatic system of the host as a primary mediator of homograft rejection. Scothorne and McGregor,[7] who pointed out that the rabbit's ear is drained unilaterally to a regional node at the base of the ear, demonstrated a marked increase in weight of that node after homografting of skin distal to it, while the contralateral node was not affected. There was no gain of weight due to the operative procedure or to absorption of toxic products from a graft that was being rejected. Furthermore, Stark and associates[9] showed that the weight gain due to homografting was significantly higher than that which follows autografting. Histologic studies[6] showed the presence of "large lymphoid cells" in the ipsilateral node after homografting. These large cells were postulated to be the site of antibody formation, which, when disseminated through the blood stream, are responsible for graft rejection. Stark and Dwyer[8] carried the argument one stage further when they showed that interruption of the lymphatic pathway by resection of the regional node produced enhanced survival of homografts. They also showed that if homografts are placed on both ears, and only 1 node resected, then both grafts are lost without enhancement. This strongly suggests that a localized connection between the graft and the lymphatic system of the host is necessary for the systemic immunologic response.

Evidence based on anatomic studies indicates that lymphatic continuity is re-established within 4 to 6 days of grafting.[1, 3, 5] One could therefore postulate a mechanism whereby homograft antigen is sequestered within the graft until lymphatic connections develop between the graft and the host's bed. The antigen is then conducted to the node where the systemic homograft response is initiated.

Certain inconsistencies are immediately apparent in this hypothesis. If immunity depends on establishment of lymphatic repair, and this takes 4 to 6 days, then it is difficult to explain nodal enlargement and histologic changes characteristic of homotransplantation which occur within 2 days of the procedure. Furthermore, it is impossible to ascribe to lymphatic mediation the rapid rejection of the "second-set" homograft.

One of these premises must be wrong. Either immunity must begin independently of lymphatic repair, or current methods of identifying lymphatics (India ink or fluo-

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*Present address: University of Colorado Medical Center, Denver, Colo.

rescein dye) do not demonstrate early functioning connections.

We decided to study the development of lymphatic repair using, as a parameter, the clearance of radioactive albumin from the intradermal tissues of the graft, since it has been shown that this protein is cleared selectively by the lymphatics rather than by capillaries.[2] Therefore, this method represents a functional rather than an anatomic approach to the timing of lymphatic re-establishment.

METHOD

For this experiment, rabbits of disparate strains (chinchillas and New Zealand whites) were used. Thirty-six animals were divided into 2 equal groups as donors and recipients, and 2 rabbits were used as controls to investigate the clearance of I^{131}-tagged albumin from the intact ear. One ear of each of 18 rabbits was injected intradermally with 0.25 ml. of I^{131}-tagged albumin containing 30 μc. The following day, with sterile technique and intravenous Nembutal anesthesia, circular full-thickness grafts measuring 2.5 cm. in diameter were taken so as to include the previously marked injection site. The grafts were transplanted immediately to the ears of 18 recipient rabbits. The purpose of the 24-hour delay was to allow intact lymphatics of the donor animal to carry away any albumin which, through faulty technique of injection, might have found its way into the subcutaneous tissue. Thus, at the time of grafting we assume that there was present only intradermally trapped albumin without contamination of the underside of the graft.

Immediately after the procedure, radioactivity was quantitated from the newly transplanted graft. A thallium-activated collimator with a 4-inch sodium iodide crystal was used, shielded with one-half inch lead through which was bored a circular aperture the size of the grafts. Each area was counted for 100 seconds. Daily readings were taken from the grafts to show clearance of albumin by the lymphatics, and from the flank of each animal to demonstrate systemic pickup of circulating I^{131}-tagged albumin.

The second part of the experiment concerned the role played by the regional auricular lymph node proximal to the graft. The day of grafting and each day thereafter, 2 rabbits underwent bilateral nodal resection. The nodes were weighed and the radioactivity measured in vitro with a well-type counter. By continuation of the count for 15 minutes, an accurate assessment could be obtained of the time when I^{131}-tagged albumin first appeared in the regional node. Furthermore, by correlation of the rate of albumin clearance from the grafts with the time of node resection, it was possible to assess the effect of nodal resection upon lymphatic clearance of protein from the grafts.

Finally, a sham operation was carried out in 2 animals, with exposure but not resection of the nodes, so as to estimate the effect that operative trauma with subsequent inflammatory reaction might have upon lymphatic clearance.

The method of graphically representing the results bears explanation. Because of the unavoidable disparity in volume of injected material, the ordinate of all grafts, representing the quantity of radioactivity present, is expressed as a percentage of initial count. The average initial raw count was between 4,000 and 6,000 counts per second. Furthermore, all counts are adjusted for radioactive decay, with a factor of 0.917 per day.

On the same graph is plotted the systemic appearance of radioactivity as measured by the same counter over the animal's flank. This, however, is presented in counts per second rather than percentage of initial count because the quantity involved is too small (up to 100 counts per second).

RESULTS

The pattern of clearance of radioactive albumin from an injection site in the intact ear conformed with the results of previous work[2] (Fig. 1).

Measurements were taken at hourly intervals for 12 hours and daily thereafter. As may be seen, there was a rapid initial loss. Fifty per cent of the injected albumin was

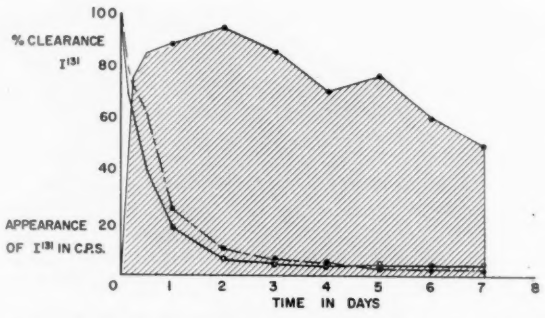

Fig. 1. The rapid rate of clearance of I^{131}-tagged albumin from the intradermal tissues of the intact ear is shown. Fifty per cent of activity is cleared within 24 hours. The solid area represents the average systemic radioactivity in counts per second.

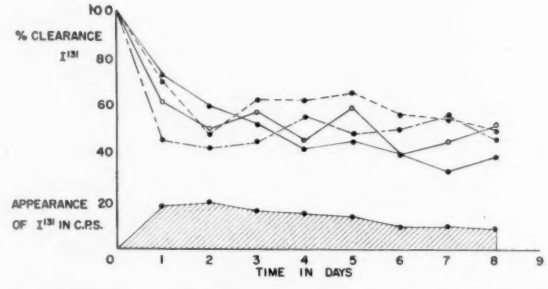

Fig. 2. The rate of clearance of I^{131}-tagged albumin from the homografts of 4 rabbits. Initial clearance takes place in the presence of an intact lymphatic system in the recipients, because they represent the late nodal resection group. Thirty-eight per cent of base-line activity is cleared within 24 hours. The solid area represents the average systemic activity in counts per second.

cleared in the first 12 hours. At the end of 8 days, only 1 to 2 per cent remained at the injection site. In counts per second this was little more than the generalized background present in the body. The level of body radiation was seen to rise correspondingly with the rapid clearance by the lymphatics, and then dwindled slowly as the protein was metabolized and excreted.

When the albumin was contained in the intradermal tissues of a graft, predictably the rate of clearance was slower. However, there was no "trapping" of albumin for several days as expected and a significant loss occurred at 24 hours. The patterns of albumin clearance from 4 animals which underwent nodal resection on the seventh and eighth posthomotransplantation days are shown in Fig. 2. Thus, the initial loss of albumin, in this series, took place in the presence of an intact lymphatic drainage system in the recipient.

As can be seen, there was an immediate loss of radioactivity from the grafts. An average of 38 per cent of base-line activity was cleared within 24 hours. The curves flattened out in 2 to 3 days. Systemic radioactivity was not elicited in the hour after the graft procedure, but was definitely present at 24 hours. The average body count at that time was 18 counts per second.

When the lymphatic drainage pathway is interrupted by surgical ablation of the regional node, the clearance of radioactive albumin is delayed significantly. Four animals underwent resection of this node either at the time of homografting or 24 hours subsequently. As can be seen (Fig. 3), the initial loss was considerably less than in the previous group. An average of 11 per cent was cleared in the first 24 hours as opposed to 38 per cent in the previous group. The curves remained shallow for 3 days, at which time they took a steeper course and then leveled off at the fifth day. Similarly, less systemic radiation was noted at first. The body count at 24 hours was only 6 counts per second and rose to a peak at 3 days. These findings—the delayed clearance of protein-bound matter after lymph node resection—provide a theoretical basis for the phenomenon of graft enhancement after regional lymph node resection.

Fig. 4 shows the superimposed mean patterns for each group, early and late node resection, which illustrate the disparity of clearance between the 2 groups. The third curve represents the pattern of clearance of 2 rabbits in which, after homotransplantation, a sham operation was carried out at the base of each ear, with exposure but not resection of the regional node. As can be seen, albumin clearance was not delayed in those animals, which demonstrates that the disparity between the groups was due to actual interference with the lymphatic system rather than to operative trauma and subsequent inflammatory reaction.

After resection of the auricular nodes from each rabbit, nodes were weighed and the amount of radioactivity determined by means of a well-type, thallium-activated sodium iodide counter. Because of the small amount of activity present, each node was counted for 15 minutes. After this, an equal time was used to measure machine and room background. The activity present is expressed in counts per second, with allowance for radioactive decay and machine background. Table I shows the results of this phase of the study.

As seen, activity was picked up by the node draining the ear which was operated upon within 2 days of grafting. That this was due to a genuine lymphatic pathway rather than to the blood stream via capillary regeneration is strongly suggested by the fact that, at that time, no activity was demonstrable in the contralateral node. In fact, throughout the experiment virtually no radiation was found on that side. The only 2 occasions were when the over-all body level was disproportionately high as seen by the irregular figures in the ipsilateral node.

Review of the nodal weights again demonstrates that the node on the homografted side increases in size more than that on the nongrafted side, confirming previous work.

SUMMARY AND CONCLUSIONS

1. Previous experiments implicate the regional lymphatic system as a primary mediator of homograft rejection. A physiologic study has been made of the time of lymphatic repair between graft and host bed.

2. The ears of 18 rabbits were injected with I^{131}-tagged albumin. The next day, full-thickness grafts were taken so as to include the injection site and were transplanted homologously. Radioactivity of the graft was measured daily to show clearance of albumin by the lymphatics and was counted from the flank to show systemic pickup. Furthermore, 2 rabbits daily underwent resection of lymph nodes. The nodes were weighed and in vitro radioactivity measured.

3. Results indicate that clearance of al-

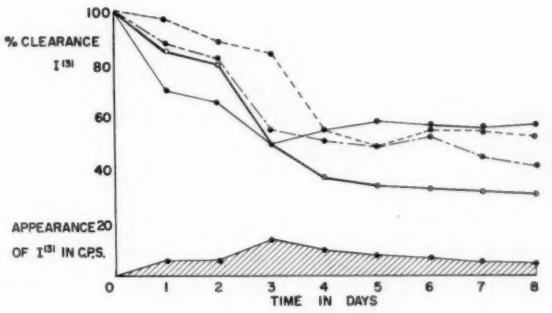

Fig. 3. The greatly impeded clearance of I^{131}-tagged albumin from the homografts of 4 rabbits which underwent lymph node resection at the time of grafting. They represent the early nodal resection group. Eleven per cent of base-line activity is cleared within 24 hours. The solid area represents the average systemic activity in counts per second and shows a slower pick-up by the body.

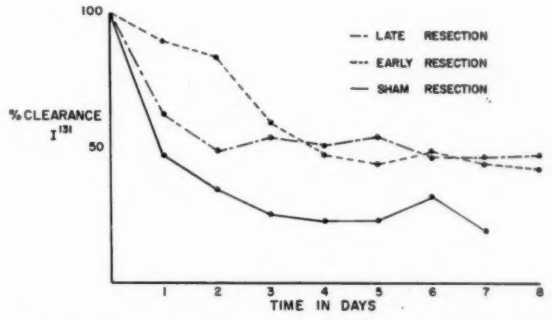

Fig. 4. The mean pattern of clearance of I^{131}-tagged albumin from both early resection and late resection groups, superimposed for comparison. The third curve shows the clearance pattern of the animals which underwent sham resection and demonstrates that clearance is not delayed by operative trauma.

Table I. *Weight and in vitro radioactivity of ipsilateral and contralateral auricular nodes*

	Grafted ear		*Nongrafted ear*	
Day	*Average weight of nodes (mg.)*	*Counts per sec.*	*Average weight of nodes (mg.)*	*Counts per sec.*
1	120	0	115	0
2	135	2	140	0
3	427	2	100	0
4	925	13	203	2
5	325	4	95	0
6	500	4	170	0
7	690	8	260	2
8	392	3	240	0

bumin begins within 24 hours of grafting. By 24 hours, between 3 per cent and 67 per cent of base-line activity was lost from the grafts, and all animals showed systemic activity. Radioactivity was found in the node at the base of the ear within 24 hours and rose to a peak at 4 to 7 days. Virtually no activity was detectable in the opposite node, indicating that clearance from the homograft was via a lymphatic pathway rather than the blood stream. The rate of albumin clearance was impeded by node resection.

4. A hypothesis which implicates the regional node in graft immunity and is dependent upon the clearance of protein-bound antigen by regenerated lymphatic connections has been proposed.

We wish to thank Dr. Richard P. Keating, Chief of the Radioisotope Laboratory at St. Luke's Hospital in the City of New York, for his helpful criticism regarding radioisotope methods.

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Experimental ascites. I. Production of ascites by gradual occlusion of the hepatic veins with an internal vena caval cannula

MARSHALL J. ORLOFF, M.D.*
GILBERT B. SNYDER, M.D.
DENVER, COLO.
From the Department of Surgery, University of Colorado School of Medicine

In 1728, Richard Lower[6] first described the experimental production of ascites in animals by occlusion of the thoracic inferior vena cava. In 1907, Bolton[1] confirmed Lower's studies and in recent years McKee and associates[9] have clearly established this technique as a simple and reliable method of producing ascites. Results of a number of studies indicate that the ascites arising from partial occlusion of the thoracic inferior vena cava is derived largely from the surface of the liver and is a consequence of obstruction of hepatic venous outflow.[2, 4, 8] Some evidence suggests that much of the ascitic fluid originates directly from the hepatic lymphatics.[3, 4, 10]

In human beings with cirrhosis of the liver, evidence indicates that obstruction of hepatic venous outflow is an important causative factor in the development of ascites, much as it is in the experimental animal. The studies of Madden and associates[7] and of Welch and his group[11] in human beings have clearly demonstrated an intrahepatic block involving the hepatic veins. However, the clinical and experimental conditions are not truly comparable because in the human being with liver disease the block involves the hepatic veins within the liver and the inferior vena caval pressure is not significantly elevated, while in the animal with partial occlusion of the thoracic inferior vena cava the obstruction is extrahepatic and produces a marked elevation of pressure in the vena cava as well as within the liver. Consequently, it has not been possible to evaluate experimentally the measures directed at decompressing the liver by shunting hepatic venous blood into the systemic venous system.

The present investigation was undertaken in an attempt to produce in dogs hepatic venous outflow obstruction comparable to that which occurs in human beings with liver disease, without producing an elevation of pressure in the inferior vena cava. It represents a modification of the technique first described in 1958 by Kling and Allen[5] and involves the insertion of a thin-walled polyvinyl cannula into the inferior vena cava at the level of entrance of the hepatic veins.

PROCEDURE

Operation. Forty-seven healthy adult male and female mongrel dogs which varied in weight from 19 to 28 kilograms were used as subjects. Anesthesia was produced intravenously with pentobarbital sodium in a dose of 30 mg. per kilogram of body weight and positive-pressure respiration was maintained with an automatic respirator which delivered a mixture of air and oxygen through an endotracheal tube. The operations were performed with sterile technique. During the operative procedure each dog received 5 per cent dextrose in water intra-

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*Markle Scholar in Medical Science. Present address: Department of Surgery, University of California School of Medicine, and Harbor General Hospital, Los Angeles, Calif.

Fig. 1. Photograph of the vena caval cannula made of dyed polyvinyl chloride. Dimensions are 3 to 3.5 inches in length, 0.025 inches in wall thickness, and 0.375 to 0.438 inches in outer diameter.

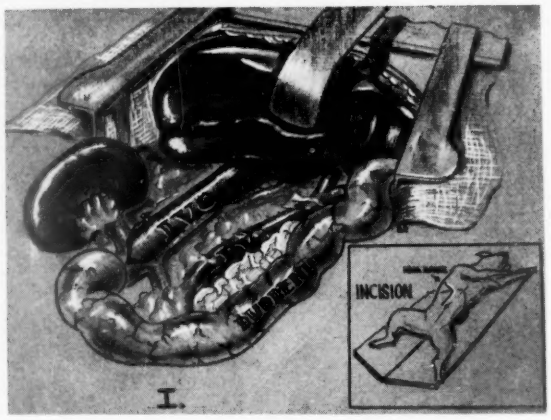

Fig. 2. Drawing which shows exposure of the abdominal inferior vena cava from the level of the renal veins to the level of its disappearance into the liver (I). The position of the dog and the right thoracoabdominal incision are shown in the inset.

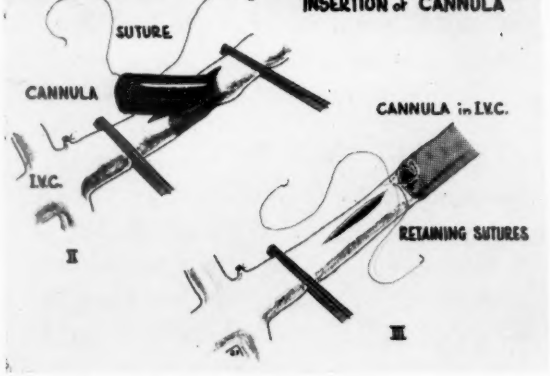

Fig. 3. Drawings which show introduction of the cannula into an incision in the anterior wall of the abdominal inferior vena cava (II), and completed insertion of the cannula which is being fixed to the vena cava by bringing the double-needle suture through the anterior wall of the vein (III). Note that the double-needle suture was attached to the inferior end of the prosthesis prior to insertion.

venously in a dose of 30 to 50 ml. per kilogram of body weight. Postoperatively food and water were offered ad libitum. All animals received procaine penicillin intramuscularly in a dose of 600,000 U. daily for 4 days including the day of operation. The cannula to be inserted into the vena cava was siliconized on its internal surface prior to operation in order to minimize clot formation in the lumen. The external surface was left unaltered for the purpose of obtaining reactive fibrosis around the hepatic vein orifices. Several types of cannulas made of polyethylene and polyvinyl chloride were tested before the procedure was standardized. The one selected for extensive trial was made of dyed polyvinyl chloride* and is employed commercially to cover electrical wires (Fig. 1). The cannulas measured 3 to 3.5 inches in length and had a wall thickness of 0.025 inches. Cannulas of 2 diameters were used, one with an outer diameter of 0.375 inches and the other with an outer diameter of 0.438 inches, the choice depending on the diameter of the vena cava. It is important to emphasize that the diameter of the cannula should be slightly smaller than that of the vena cava and the cannula should slide easily into the vessel. A tight-fitting cannula invariably produces acute occlusion of the hepatic veins and death.

The dog was placed in the left oblique position for a right thoracoabdominal incision. A pad was placed under the animal at the level of the costal margin. The incision extended through the right tenth intercostal space, across the costal cartilages, and onto the abdominal wall as a right rectus incision (Fig. 2). The diaphragm was incised along the lines of its fibers from the periphery to the central tendon and the wound edges were held widely apart with a self-retaining retractor. The abdominal vena cava was mobilized from the level of the renal veins to the level of its disappearance into the liver (Fig. 2).

*Natvar "400" tubing made by Natvar Corp., Woodbridge, N. J., and supplied by Electrical Specialty Co., Denver Colo.

Prior to insertion of the cannula an atraumatic swaged No. 5-0 silk suture with needles attached to both ends was placed through the distal end of the cannula for subsequent fixation of the tube to the wall of the vena cava. Before insertion of the prosthesis, heparin in a dose of 1 to 1.5 mg. per kilogram was administered intravenously. In early experiments, protamine in an intravenous dose of 2.0 mg. per kilogram was given before the wound was closed, but in later studies administration of protamine was abandoned.

The abdominal vena cava was occluded with vascular clamps at 2 levels, just inferior to the liver and just above the renal veins, and a 2 cm. longitudinal incision was made in its anterior wall between the 2 clamps. The cannula was inserted into the opening in the vena cava and the abdomen was filled with an isotonic saline solution containing heparin (20 mg. per 100 ml. of saline) until the vena cava was completely submerged (Fig. 3). The superior clamp was then removed and the cannula was pushed cephalad into the vena cava until its inferior end was just superior to the upper limit of the incision in the vena cava. The superior end of the cannula extended well into the thoracic inferior vena cava above the level at which the superior hepatic vein entered. The cannula was fixed to the vena cava by bringing the double-needle suture through the anterior wall of the vein and tying its ends (Fig. 3). Failure to suture the cannula to the wall of the vessel leads to migration of the tube into the right auricle. The opening in the vena cava was occluded with a Satinsky clamp, vena caval blood flow was restored by removal of the inferior vascular clamp, and the incision in the vein was approximated with a continuous No. 5-0 vascular silk suture (Fig. 4). The incisions in the diaphragm and in the thoracic and abdominal walls were closed in layers with chromic catgut sutures and the costal cartilages were approximated with heavy silk sutures. The skin edges were approximated with sutures of fine silk. A large rubber tube was left in the pleural cavity

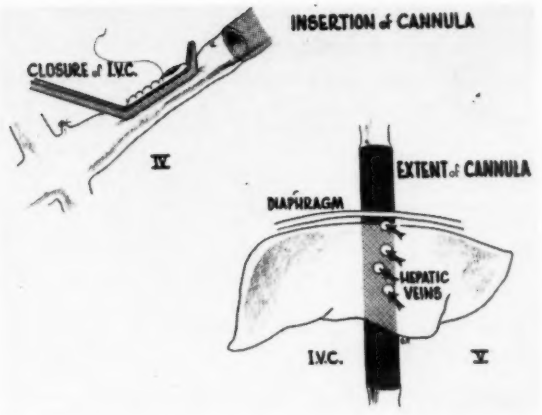

Fig. 4. Drawings which show closure of the vena caval incision over a Satinsky clamp after the blood flow has been restored (IV), and the completed operation with the cannula in position opposite the orifices of the hepatic veins (V).

until the closure of the wound was completed when, after aspiration of the pleural cavity, it was removed.

Pressures. Pressures in the abdominal inferior vena cava and portal vein were determined by needle puncture during operation and before and after insertion of the cannula. A spinal manometer filled with a heparin-saline solution was employed and the level of the vein in which pressure was being measured was used as the reference point. In 4 animals, pressure determinations were repeated 1 to 4½ months after operation.

Angiograms. Inferior vena caval angiograms were obtained from 3 weeks to 10 months postoperatively from most of the animals which survived for more than 2 weeks. The dogs were lightly anesthetized intravenously with pentobarbital sodium and a polyethylene catheter was inserted through a saphenous vein into the inferior vena cava to a level just superior to the entrance of the renal veins. Seventy per cent Urokon in a dose of 25 ml. was injected rapidly and 8 roentgenograms were obtained serially at 1-second intervals.

Paracentesis. All animals were subjected to abdominal paracentesis when ascites was apparent clinically and the amount of fluid obtained was measured. Subsequently, paracentesis was repeated intermittently. Para-

Table I. *Pressures in abdominal inferior vena cava and portal vein immediately before and after insertion of cannula in 47 dogs*

	Control pressure (cm. saline)		*Pressure after cannula inserted (cm. saline)*				*Pressure change (cm. saline)*	
	Mean	*Range*	*Mean*	*Range*	*% animals*		*Mean*	*Range*
Inferior vena cava	7.5	2.0-13.0	3.8	1.0- 9.2	Fall	98	3.7	0.4-8.4
					No change	2	—	—
					Rise	0	—	—
Portal vein	11.5	6.0-15.0	13.5	8.0-21.0	Fall	4	0.6	0.4-0.7
					No change	15	—	—
					Rise	81	2.5	0.3-7.0

Table II. *Pressure measurements in abdominal inferior vena cava and portal vein in 4 dogs, repeated 1 to 4½ months after insertion of cannula*

Dog No.	*Cannula patency*	*Interval between measurements (mo.)*	*Pressures (cm. saline)*					
			Inferior vena cava			*Portal vein*		
			Initial	*Repeat*	*Change*	*Initial*	*Repeat*	*Change*
59-423	Patent	1	3.5	3.0	–0.5	14.5	26.5	+12.0
60-22	Patent	4½	2.5	3.0	+0.5	13.5	23.4	+ 9.9
60-43	Occluded	4½	4.0	8.0	+4.0	15.3	27.0	+11.7
60-176	Occluded	2½	8.0	10.0	+2.0	15.5	25.6	+10.1

centesis was performed with a large trocar under local procaine anesthesia. The animal was placed in the prone position on a special table containing an opening through which the abdomen could be drained from a position underneath the table.

Autopsies. All animals died or were sacrificed and were subjected to autopsy examinations. In each dog the viscera were studied grossly and particular attention was given to the liver and to the vena cava containing the prosthesis. Sections of liver were examined microscopically.

RESULTS

Mortality rate. Thirty-three animals failed to survive for sufficiently long periods of time to develop ascites. The majority of these (76 per cent) died within 48 hours of operation and at autopsy the liver was found uniformly to be enlarged and congested. It is believed that death was a consequence of acute occlusion of the hepatic veins from a tight-fitting cannula. Four animals died from wound infections or pneumonia, 1 dog was lost, and the cause of death could not be determined in 3 dogs which died during the first postoperative week.

Fourteen animals (30 per cent) lived for 3 weeks to 10½ months and were considered long-term survivors in that they were alive for a sufficient length of time to have developed ascites. Six of these died from 21 to 60 days postoperatively as a result of inanition associated with massive ascites. The remaining 8 dogs were sacrificed 5 weeks to 10½ months postoperatively.

Pressures. In all but 1 of the 47 dogs there was a fall in abdominal inferior vena caval pressure after insertion of the cannula (Table I). In 1 animal there was no change in pressure. The mean pressure decrease was 3.7 cm. saline and the range was 0.4 to 8.4 cm. There was no significant difference in the magnitude of the drop in pressure in the dogs which subsequently died and in those which survived. The fall in vena caval pressure is believed to have resulted from a decrease in the flow of hepatic venous blood into the vena cava as a consequence of obstruction of the hepatic vein orifices by the prosthesis.

The portal venous pressure increased after insertion of the cannula in 38 of 47 animals (81 per cent, Table I). The mean rise was 2.5 cm. saline and the range was 0.3 to 7 cm. Again, there was no significant difference between dogs which died and those which lived. In 5 dogs no change in pressure was found and in 2 dogs there was a slight pressure drop of less than 1 cm. Hepatic venous outflow obstruction with back pressure on the liver and portal venous system is believed to have been responsible for the rise in portal pressure which occurred in the majority of animals.

In 4 animals pressures in the inferior vena cava and portal vein were again determined just prior to sacrifice 1 to 4½ months after operation (Table II). Two of these animals had a patent cannula and 2 had developed thrombosis of the prosthesis. In all 4 animals the portal venous pressure had increased markedly to hypertensive levels as a result of progressive hepatic venous outflow obstruction. The rise ranged from 9.9 to 12 cm. saline above the final level obtained at the time of operation.

In the dogs with a patent cannula the inferior vena caval pressure had not changed significantly. In 1 dog there was a 0.5 cm. rise and in the other a 0.5 cm. fall in pressure. In the 2 animals with thrombosis of the cannula, the vena caval pressure was found to have increased 4 cm. in one and 2 cm. in the other. The rise was not nearly as great as might be expected, probably because of the profuse collateral circulation which had developed.

Ascites. Twelve of 14 long-term survivors developed massive ascites (Table III). The ascites was first detected clinically between 9 and 44 days postoperatively and varied in amount from 1.5 to 11.5 L. (Fig. 5). The

Table III. *Onset and magnitude of ascites and patency of cannula in long-term survivors*

Dog No.	*Clinical onset ascites (postoperative day)*	*Volume of fluid (ml.)*	*Angiogram*	*Time of death and cause*	*Autopsy findings*
59-122	21	6,000	—	21 days, inanition	Cannula patent
59-130	14	2.300	—	21 days, inanition	Cannula patent
59-131	34	10,000	Cannula patent	2 mo., inanition	Cannula patent
59-261	13	1,500	Cannula blocked	10½ mo., sacrificed	Thrombus in cannula
59-423	9	4,000	Cannula patent	1 mo., inanition	Cannula patent
60-22	38	4,000	Cannula patent	4½ mo., sacrificed	Cannula patent
60-43	31	3,000	Cannula blocked	4½ mo., sacrificed	Thrombus in cannula
60-59	44	3,000	Unsuccessful	51 days, inanition	Cannula lost
60-141	40	2,800	—	2 mo., inanition	Cannula patent
60-143	None	—	Cannula blocked	3 mo., sacrificed	Low insertion of cannula, superior hepatic vein open, thrombus in cannula
60-176	25	11,500	Unsuccessful	2½ mo., sacrificed	Thrombus in cannula
60-188	None	—	Cannula blocked	2½ mo., sacrificed	Low insertion of cannula, superior hepatic vein open, thrombus in cannula
60-246	30	1,800	Unsuccessful	5 weeks, sacrificed	Thrombus in cannula
60-XXX	30	3,000	—	6 mo., sacrificed	Thrombus in cannula
Summary	9-44 days	1.5-11.5 L.	43% patent	—	46% patent

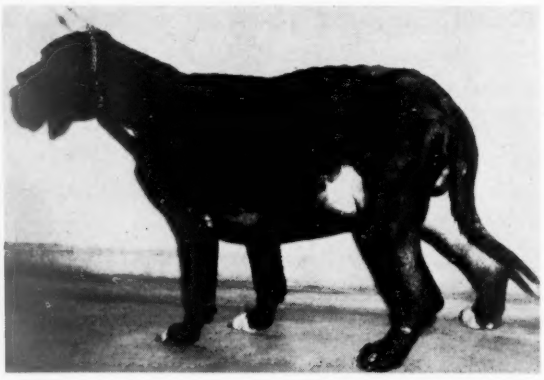

Fig. 5. Photograph of dog No. 59-131 taken 45 days after insertion of the internal vena caval cannula shows massive ascites. Immediately after the photograph was taken, paracentesis produced 10 L. of ascitic fluid.

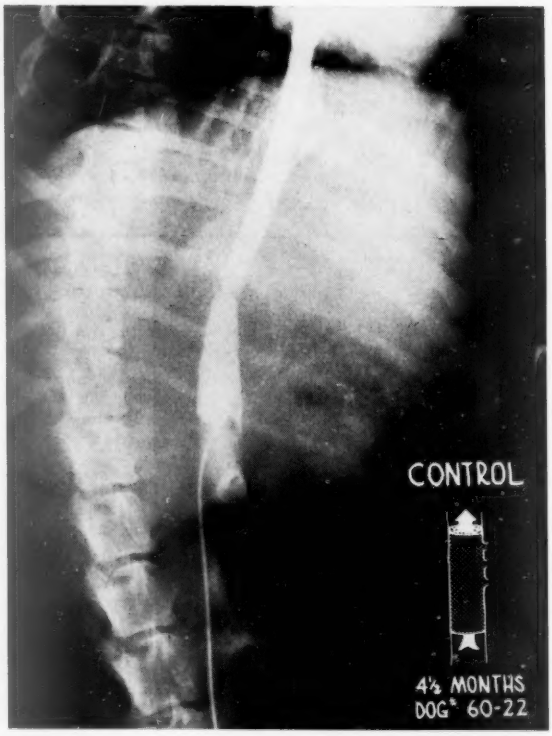

Fig. 6. Vena caval angiogram from dog No. 60-22 performed 4½ months after operation shows a patent cannula with rapid passage of dye into the heart. The catheter was positioned about 2 inches below the cannula. The animal had 4 L. of ascitic fluid at the time of this study.

fluid was straw colored and had the typical composition of a transudate of plasma. Once ascites developed, it persisted until the animal died or was sacrificed. Six dogs died from 21 to 60 days postoperatively as a result of inanition associated with the ascites, while the remaining 8 animals were sacrificed from 5 weeks to 10½ months after operation.

The failure to produce ascites in 2 animals was clearly explained by autopsies which in both cases showed that the cannula had not been inserted sufficiently high in the vena cava and had failed to occlude the large superior hepatic vein.

Angiograms. Inferior vena caval angiography was attempted in 10 animals from 3 weeks to 10 months postoperatively. In 3 dogs the procedure was unsatisfactory, while in 7 animals adequate visualization of the vena cava was obtained. The cannula was found to be patent in 3 animals (43 per cent), 3 weeks, 1 month, and 4½ months, respectively, after operation (Fig. 6), and was occluded in 4 animals. In each instance of occlusion, the block was demonstrated at the inferior end of the prosthesis and numerous large collateral vessels were seen bypassing the obstruction (Fig. 7).

Autopsies. Postmortem examinations were performed in all animals. In 1 of the 14 long-term survivors the cannula was lost during the autopsy and it is not known whether or not the cannula was patent. In 6 of the remaining 13 dogs (46 per cent), the cannula was found to be patent from 21 days to 4½ months postoperatively while in 7 animals studied 5 weeks to 10½ months after operation, the prosthesis was found to be completely occluded by an organized thrombus (Table III). Numerous large collateral veins attached to the vena cava below the level of the cannula were observed in animals in which thrombosis had occurred.

In each instance the cannula was surrounded by a smooth, shiny neointima of fibrous material which completely occluded the orifices of the hepatic veins. In 2 dogs which failed to develop ascites because of low insertion of the prosthesis, the orifice of the large superior hepatic vein was open.

In all animals the liver was greatly enlarged, hard, and congested and fibrinoid material was deposited on its surface. Mas-

sive ascites was present in all but the 2 dogs referred to previously. Microscopic examination of the liver showed dilatation of the entire hepatic vasculature, intense congestion of the sinusoids, dilatation of the lymphatic spaces, and focal areas of necrosis.

DISCUSSION

The insertion of a polyvinyl cannula into the inferior vena cava at the level of entrance of the hepatic veins is a simple method of producing ascites by gradual selective occlusion of the hepatic venous outflow tract. The reactive material of which the cannula is made stimulates the formation of a fibrous neointima which surrounds the prosthesis and completely covers the orifices of the hepatic veins. The ascites which develops is massive and persistent. The hepatic venous outflow obstruction leads to progressive portal hypertension. The mechanism by which ascites is produced, therefore, is similar to that which is believed to occur in human beings with ascites due to cirrhosis of the liver. In a significant number of animals, 46 per cent in this study, the cannula remains patent for long periods and when such is the case, the pressure in the inferior vena cava is normal. In this regard, the method affords a distinct advantage compared to the technique of partial thoracic inferior vena caval occlusion which by its nature results in marked elevations of inferior vena caval pressure.

There are 2 problems associated with the internal cannula technique of producing ascites, namely, acute hepatic venous occlusion and thrombosis of the cannula. The first difficulty, acute occlusion of the hepatic veins, results from a cannula which fits too tightly in the vena cava and it is followed invariably by death within 24 to 48 hours. It is believed that acute hepatic venous outflow obstruction was responsible for most of the deaths in this study. It is desirable to use a prosthesis which slides easily into the vein but at the same time fills the lumen, since small cannulas which fit loosely in the vena cava rapidly develop thromboses. Unfortunately, it is often not possible during the operation to determine accurately when the cannula is producing too much obstruction of hepatic venous outflow.

The second problem, thrombosis of the cannula, is a consequence of the introduction of a foreign body into the low-flow, low pressure vena cava. Clot formation has been a major stumbling block associated with the use of synthetic materials in the venous system and the development of occlusion of the prosthesis in a number of the animals was not surprising. Indeed, it was surprising that so many of the cannulas (46 per cent) remained patent for long periods of time. Perhaps siliconizing the internal surface of the cannula and the use of systemic heparinization increased the incidence of success.

Although thrombosis of the cannula and

Fig. 7. Vena caval angiogram from dog No. 60-43 performed 4½ months postoperatively shows thrombosis of the cannula and large collateral vessels bypassing the obstruction. The collateral vertebral veins are particularly prominent. The roentgenogram shown was the first in the series. The dye had disappeared from the vena cava 3 seconds later, indicating efficient function of the collateral vessels. The animal had 3 L. of ascitic fluid.

the resultant vena caval obstruction did not seem to increase or decrease the rate of ascitic fluid formation, it would be expected to nullify the main advantage of the internal cannula technique. It is of interest, therefore, that in the 2 dogs in which pressure determinations were repeated some time after the development of thrombosis, the vena caval pressures had increased only slightly (2 and 4 cm.). Gradual development of thrombosis and development of an extensive collateral circulation are presumed to have prevented a marked increase in vena caval pressure. The most prominent collateral pathways involved the vertebral and spinal veins.

With the exception of the internal vena caval cannula technique, no simple method of producing ascites has been described by which hepatic venous outflow is selectively obstructed, inferior vena caval pressure is not elevated, and consistently massive ascites is produced. Although problems such as thrombosis of the cannula and death from acute hepatic venous occlusion often complicate the use of the internal cannula method, the results of this investigation indicate that further use of this technique is warranted, particularly as a tool for investigating the effects on ascites of various portal-systemic venous shunts.

SUMMARY AND CONCLUSIONS

A simple method for producing ascites by gradual occlusion of the hepatic veins without obstruction of the inferior vena cava was evaluated in 47 dogs. The technique involved the introduction of a thin-walled polyvinyl cannula into the inferior vena cava at the level of entrance of the hepatic veins. The reactive polyvinyl stimulated the gradual formation of a fibrous neointima which completely covered the orifices of the hepatic veins.

After insertion of the prosthesis there was a fall in inferior vena caval pressure in 98 per cent of the animals, presumably because of obstruction of the flow of hepatic venous blood into the vena cava. At the same time, there was a rise in portal venous pressure in 83 per cent of the dogs, believed due to hepatic venous outflow obstruction with back pressure on the portal system. Determination of pressures again after long intervals of time in 4 dogs showed a progressive elevation of portal pressure in all, no change in vena caval pressure in the 2 animals with a patent cannula, and a slight rise in vena caval pressure in the 2 dogs with thrombosis of the cannula.

Fourteen animals survived the operation for significant periods. The majority of animals which failed to survive died within 48 hours, presumably from acute occlusion of the hepatic veins due to a tight-fitting cannula. Twelve of the 14 long-term survivors developed massive persistent ascites varying in amount from 1.5 to 11.5 L. within 9 to 44 days postoperatively. The 2 animals which failed to develop ascites were found to have patent superior hepatic veins as a result of insertion of the cannula too low in the vena cava.

Angiograms and autopsies showed a patent cannula in 46 per cent of the surviving animals for periods of up to 4½ months. In the remainder of the dogs, the cannula developed thrombosis.

Despite the problems of acute hepatic venous occlusion and thrombosis of the cannula, the incidence of success is sufficiently high to warrant further use of this technique, particularly as a means of studying the effects on ascites of portal-systemic shunts. No other technique is available presently for this purpose.

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Coagulation studies on bleeding surgical patients

KARL E. KARLSON, M.D.
BERNARD LERNER, M.A.
BROOKLYN, N. Y.
From the Department of Surgery, State University of New York Downstate Medical Center, and Kings County Hospital

Studies reported here concern a group of patients admitted to the hospital with gastrointestinal hemorrhage and another group with excessive uncontrollable oozing during operation. The tests used in these studies for the various components of the coagulation mechanism are of such nature that they may be performed relatively quickly without elaborate equipment or extensive special knowledge. Therefore, they may be applicable to the evaluation of these problems on a routine basis.

It is generally accepted that most gastrointestinal hemorrhage results initially from involvement of blood vessels in the local lesion. Prolongation of the bleeding may disturb physiologic processes and alter certain components of the coagulation mechanism. In patients with excessive oozing during or immediately after operation, this bleeding from small vessels has been demonstrated in some cases to be associated with defects in the coagulation mechanism.

The coagulation tests used were chosen because they indicate the nature of many of the possible deficiencies in the clotting mechanism. A knowledge of an existing deficiency allows intelligent use of one or more of the specific therapeutic agents which have been advocated in the literature for these deficiencies. For example, vitamin K is effective for prothrombin and factor VII deficiencies in the presence of adequate liver function. Fibrinogen administration has been advocated for hypofibrinogenemia. Albumin has been suggested to supply antifibrinolysin (antiplasmin) since this enzyme is contained in the albumin fraction of the plasma. Platelet transfusions are used in cases of severe platelet deficiency. Fresh blood and fresh frozen plasma are usually effective for deficiencies in platelets (fresh blood only contains platelets), factor V, and other constituents of phase I of the coagulation mechanism. Fresh blood and fresh frozen plasma are generally helpful in bleeding due to all possible coagulation causes when the defects are severe or not definitively understood.

The coagulation abnormality most frequently reported during gastrointestinal bleeding from otherwise benign disease processes is prothrombin deficiency, and somewhat less often factor V and platelet deficiencies. Occasionally abnormal results have been observed in almost all of the other usual coagulation measurements.[1, 6, 10, 29] Some of the deficiencies have been of severity commonly implicated as dangerous, but in most of the cases reported the patients appeared to have had no serious impairment of hemostasis.

Patients with gastrointestinal bleeding and associated liver diseases show an even greater incidence of abnormality. Low prothrombin values, prolonged recalcification times, decreased factor V, prolonged thrombin times, low platelet counts, low fibrinogen levels,

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and fibrinolysis have been commonly found in patients with liver disease.[1, 6, 10, 15, 21, 28, 30, 33, 38] The role of the liver in production of prothrombin, factor V, fibrinogen, and other factors determines this relationship.

Decreased blood flow to the liver with accompanying hepatic anoxia has been demonstrated during hemorrhage from the gastroduodenal artery.[23] However, a detrimental effect on coagulation from liver hypoxia during upper gastrointestinal bleeding has not been shown.

With surgical oozing, decreased numbers of platelets are frequently observed, but in most cases they are not decreased sufficiently to explain the abnormal bleeding.[13, 14, 20, 40, 43, 45] Measurements which reflect platelet decreases, such as clot retraction, bleeding time, tourniquet test, and prothrombin consumption have been noted to be correspondingly affected.[40]

Decreased fibrinogen levels are reported by several groups in some, but not all, patients with oozing. Afibrinogenemia is almost never seen in surgical patients.[8, 31, 43, 45] Fibrinolysis has been observed in patients with oozing.[7, 8, 13, 24, 31, 40, 43, 45] This is thought to have little clinical importance by some,[40, 43] whereas others consider it to be an etiological factor in the bleeding.[7, 45]

Factor V deficiency has been reported to occur more frequently in patients with oozing than in those without.[45] Abnormalities in several measurements (platelets, recalcification time, thromboplastin generation, prothrombin consumption, prothrombin activity, fibrinogen, and fibrinolysis) were shown to be similar in one study of patients with oozing and a control group of patients without, and the conclusion was drawn that unevaluated factors were involved in the former group.[43]

While oozing has been known to be closely associated with massive blood transfusions of approximately 5,000 ml. or more, it has not been demonstrated that this is a consistent relationship.[17, 20, 40, 43, 45] Transfusion reactions have been cited as the basis for the development of oozing,[12, 13, 26] while some authors have questioned the role of transfusion reactions.[45] A heparinoid substance has been related to oozing.[12] It has been demonstrated that the citrate from large infusions of bank blood will not cause oozing.[45]

It does not appear that a single coagulation abnormality can be demonstrated to be the common cause for oozing.[43, 45] It has been indicated, however, that oozing is more frequently associated with multiple coagulation abnormalities.[45]

METHODS AND MATERIALS

Analytically, 11 tests were employed to detect vascular and coagulation defects. These tests and their general relationship to the blood and tissue coagulation mechanisms are illustrated by the form used by the laboratory to report results (Fig. 1). It is useful to note that some measurements reflect defects in both vascular integrity and coagulation mechanism, and some measurements reflect defects in more than one phase of coagulation.

Bleeding time. The method of Ivy was used.[27] Normal was 1 to 5 minutes. Occasionally the method of Duke was employed.[19, 32] Normal was 1 to 3 minutes. Three millimeter lancets were used.*

Tourniquet test. The positive pressure method for 5 minutes was used[19, 27] (normal, no petechiae).

Clotting time. The clotting-time test was performed by a 3-tube Lee-White method.[22] Modifications were a 2-syringe technique, a 38° C. bath, and no saline in the syringes or tubes. Normal was 5 to 10 minutes for the third tube.

Clot retraction. Retraction in the clotting-time tubes was judged after 1 hour at 38° C. Retraction was graded "good" when the clot occupied one-half to two-thirds of the total volume,[25] "fair" for lesser degrees of retraction, and "poor" for no retraction. "Good" retraction was normal.

Platelet smear. A Wright-stained smear was examined under oil immersion (×970).[19, 27] Two per high power field (about 100 red blood cells per field) was adequate.

*Medi-Point Lancets, Brooklyn, New York.

BLOOD COAGULATION REPORT

Patient's Name: _____ Date: _____

Ward: _____ Age: _____ Sex: _____ Time: _____

_____

_____

VASCULAR*

Bleeding Time: _____ Normal: 1-5 min. (Ivy)
1-3 min. (Duke)

Tourniquet Test: _____ Normal: No petechiae

PHASE I. BLOOD OR TISSUE THROMBOPLASTIN FORMATION

Prothrombin Consumption: _____ Normal: 85-99%

Clotting Time (Lee-White 38° C.): _____ Normal: 5-10 min. 3rd tube

Clot Retraction (1 hr. 38° C.): ☐ GOOD ☐ FAIR ☐ POOR

Platelet Smear: _____ "Adequate": 2/HPF (100 RBC/HPF)

Factor V Corrects Proth. Act. to: _____ % of control

Factor VII Corrects Proth. Act. to: _____ % of control

Deficient: Corrects prothrombin activity more than halfway to 100%

PHASE II. THROMBIN FORMATION

Prothrombin Activity: Control: _____ secs. _____

Patient: _____ secs. = _____ % of control
Normal: 65-100%

PHASE III. FIBRIN FORMATION

Fibrinogen: _____ Normal: 180-390 mg.%

Fibrinolysis (24 hrs. 38° C.): _____ Negative: No lysis in 24 hrs.

*Some measurements reflect vascular structure and coagulation mechanism. Some measurements reflect more than one phase of coagulation.

Fig. 1. Blood coagulation report form.

Prothrombin activity. The Quick[32] method was used, but with 8 mm. inner diameter tubes. Simplastin* was the thromboplastin source, and Protrol† served as the control plasma. The per cent of control was obtained from a dilution curve supplied with the Simplastin. Normal was 65 to 100 per cent, which corresponds to about 3 seconds over control.[9, 16]

Factor V deficiency.[4, 5, 39] When the prothrombin activity was less than 65 per cent, the ability of factor V to correct the abnormality was determined by dilution of the plasma with prothrombin-free plasma (P.F.P.)‡ and determination of the prothrombin activity of the dilution (80 per cent P.F.P. and later 50 per cent P.F.P. dilution was used). Factor V deficiency is considered to be present when the abnormal prothrombin activity is corrected by the addition of P.F.P. (factor V) more than halfway toward 100 per cent from the uncorrected value.

Factor VII deficiency.[4, 39] When factor V correction of prothrombin activity was inadequate, the ability of factor VII to correct the abnormality was determined by dilution of plasma with normal serum§ (9 to 1), and determination of prothrombin activity of the dilution. Factor VII deficiency is considered to be present when abnormal prothrombin activity is corrected by the addition of serum (factor VII) more than halfway toward 100 per cent from the uncorrected value. (Note: Adequate correction by either factors V or VII implies a normal prothrombin content and a normal content of the other factor. Inadequate correction by both factors implies a deficiency in prothrombin, prothrombin plus factors V and/or VII, or in factors V plus VII).

Prothrombin consumption.[32, 41] Serum prothrombin activity was determined on serum from the clotting-time tubes after 1 hour at 38° C., but 0.1 ml. P.F.P. was blown into the Simplastin just before addition of the serum. The per cent prothrombin consumption equals 100 per cent less the per cent serum prothrombin activity. Normal was 85 to 99 per cent, which corresponds to serum prothrombin time of about 25 seconds or higher (Protrol, 11 to 12 seconds).

Fibrinogen (method I). The method up to the formation of the Biuret color is essentially that of Ratnoff and Menzie.[34] The color was developed by the addition of 4.0 ml. of saline, followed by 5.0 ml. of dilute biuret reagent,[44] and allowing the solution to stand 30 minutes in a 38° C. bath. Absorption was measured in a Coleman 14 spectrophotometer at 550 mu., and the fibrinogen concentration calculated on the basis of a bovine albumin* calibration curve. Normal was 180 to 390 mg. per cent.

Fibrinogen (method II). Later determinations were performed by a serial dilution method,[35] which was calibrated by the use of saline-diluted human plasma against method I. Titers of 32, 64, and 128 consistently corresponded to values of 100, 150, and over 200 mg. per cent fibrinogen. The use of freshly dissolved thrombin (in saline) was important in this range. Normal was a titer of 128 (tube 7) equal to over 200 mg. per cent.

Fibrinolysis. Fibrinolysis was detected by observation of the clotting-time tubes in a 38° C. bath for 24 hours[39] (negative, no lysis).

Clot lysis was adopted as the determination of choice for clinical purposes because fibrinolytic enzymes with activity insufficient to effect clot lysis are probably insignificant clinically as the cause of bleeding.[39] Therefore, the more elaborate methods for detection of profibrinolysin, fibrinolysin, antifibrinolysin, and other proteolytic enzymes were not employed.

Blood volume. Blood volumes were determined by I^{131} and hematocrit.[36] Lowest normal red blood cell mass (R.C.M.) was considered to be 30 ml. per kilogram.

*Simplastin, Warner-Chilcott Laboratories, Morris Plains, N. J.

†Protrol, Knickerbocker Biologicals, New York, N. Y.

‡Prothrombin-Free Beef Plasma (P.F.P.), Hyland Laboratories, Los Angeles, Calif.

§Normal serum. Blood clotted 2 hours at 38° C., and serum separated and frozen in aliquots at −20° C.

*Pro-Sol, Standard Scientific, New York, N. Y. Vendor analysis for Kjeldahl nitrogen.

Table I. *Diagnostic classification of 143 patients with gastrointestinal bleeding*

Diagnosis	*No. of patients*
Benign Lesions	
Duodenal ulcer	50
Gastric ulcer	26
Marginal ulcer	3
Hiatus hernia	3
Gastritis	2
Enteritis	2
Duodenal adenoma	1
Cholecystitis	1
Sigmoid diverticulosis	2
Colonic polyps	2
Colonic bleeding	3
Internal hemorrhoids	1
Bleeding site unknown	14
Total	110
Malignant lesions	
Carcinoma of stomach	6
Carcinoma of colon	6
Carcinoma of rectum	7
Total	19
Associated hepatic disease	
Cirrhosis	10
Metastatic carcinoma to liver	3
Hepatomegaly (cause undetermined)	1
Total	14
Three-Group total	143

Gastrointestinal hemorrhage. Diagnostically, the patients with gastrointestinal hemorrhage were classified into 3 groups (Table I). These groups were composed of patients with (1) benign lesions, (2) malignant lesions, and (3) associated hepatic disease.

Laboratory estimation of blood volumes on 134 of the patients showed an average red blood cell mass (R.C.M.) of 16.4 ml. per kilogram, which represents a blood loss of 45 per cent of normal[18] (Table II). Sixty-two per cent of these patients had a red blood cell mass less than 18 ml. per kilogram, equivalent to an average blood loss of 40 per cent.

Blood transfusion, except in the hepatic disease group, was infrequent before coagulation studies were performed. Only 17 per cent of all the patients had received blood before analysis. The average transfusion was 1,600 ml., a quantity which is usually not considered detrimental to the coagulation processes.

The relative amounts of blood loss indicated in Table II for the 3 groups are the result of the methods employed for patient selection and might be different under other circumstances.

Surgical oozing. Twenty patients who bled excessively from small vessels during operation or the postoperative period were studied for coagulation or vascular defects (Table III). The bleeding was in all cases of the small-vessel oozing type and was considered excessive for the operation being performed. Descriptions of the oozing came from the surgeons involved and from the patients' charts. Although simultaneous large vessel bleeding did occur in some of the cases, troublesome excessive small vessel oozing was present in every case. All analytical work was carried out while the patient was experiencing the excessive oozing, but not always at the most critical period of the episode.

Table III is arranged in order of increasing blood transfusion received up to the time of analysis. The average amount of blood received was 5,600 ml. Ten of the patients received less than 5,000 ml. when coagulation studies were performed. Almost all of the patients received additional blood before the oozing episode was over, so that total amounts for the episodes are somewhat higher.

Oozing was first noted during operation in 13 of the 20 patients, and in the other 7 almost immediately postoperatively. Three analyses were performed while the operation was in progress, 9 the day of operation, and 4 each the first and second days postoperatively.

The oozing was controlled in 18 of the 20 patients within 1 day of the analytical work. Two patients continued oozing up until the time they died on the day of operation. They had been given apparently adequate blood replacement throughout. Three more patients died within 3 days of operation, but the oozing had been previously controlled. Of the 5 patients who did not survive, 4 had received over 10,000 ml. blood at the time of analysis.

In addition to the bank blood, fresh blood was administered to 6 patients (Patients 8, 11, 12, 14, 15, and 19), and fresh frozen plasma to 2 others (Patients 1 and 13). Vitamin K was given whenever abnormal prothrombin activities indicated the necessity. A multivitamin preparation (containing vitamin C) was routinely given all patients postoperatively.

RESULTS

Gastrointestinal hemorrhage. The frequency of abnormal results of coagulation measurements among the 3 groups of patients with gastrointestinal bleeding is shown in Table IV. The 110 patients with benign lesions suffered only 5 per cent abnormal coagulation measurements, and the 19 patients with malignant lesions only 8 per cent.

The most frequently abnormal measurements in patients with benign lesions were prothrombin consumption (abnormal in 16 per cent), and prothrombin activity (abnormal in 12 per cent). In the patients with malignant lesions, the greatest number of abnormalities occurred in the same 2 measurements, but to a slightly greater extent. Prothrombin consumption was decreased in 22 per cent of the patients and prothrombin activity in 16 per cent.

It is apparent from Table IV that the bleeding patients who had associated hepatic disease showed considerably more abnormal measurements (22 per cent) than did the others. The 2 tests most frequently abnormal were the same ones as in the other 2 groups, but in reversed order—prothrombin activity (abnormal in 71 per cent), and prothrombin consumption (abnormal in 40 per cent).

Of the 10 patients with hepatic disease, the decreased prothrombin activities in at least 3 were due to factor V deficiency and in 1 to factor VII deficiency. Two of the abnormal prothrombin consumptions were caused by factor V deficiency (cirrhosis), and the other 2 were due to defects in nonspecified phase I factors, antihemophilic globulin, plasma thromboplastic component, or others (metastatic hepatic carcinoma).

Examination of the available records of 85 of these patients was made to determine the presence of clinical shock at or immediately prior to the time of coagulation studies. Of 19 patients in shock, 8 (42 per cent) had 1 or more abnormal result of coagulation tests and 3 (16 per cent) had 2 or more abnormal results. Of 66 not in shock, 17 (26 per cent) had 1 or more abnormal test result and 7 (11 per cent) had 2 or more abnormalities. Prothrombin consumption was abnormal in 3 of 10 patients without obvious liver disease in shock in whom the test was performed, and in 2 of 22 similar patients not in shock.

Surgical oozing. The analytical data for the 20 patients who oozed abnormally during operation are shown in Table V. Only 1 patient displayed no coagulation disturbance whatever. A total of 189 measurements were performed on these 20 patients. Sixty (32 per cent) of the 189 values were abnormal.

Sixteen per cent of the measurements were abnormal in the group of 10 patients who received less than 5,000 ml. of blood, whereas 47 per cent of the measurements

Table II. *Evaluation of blood loss in patients with gastrointestinal bleeding*

Diagnostic group	*No. of patients*	*Average R.C.M. (ml./Kg.)*	*% patients with R.C.M. < 18 ml./Kg.**	*% of patients transfused†*
Benign lesions	110	15.2	67	15
Associated hepatic disease	14‡	18.5	60	50
Malignant lesions	19	21.7	32	11
	Average	16.4	62	17

*An 18 ml. per kilogram red blood cell mass (R.C.M.) represents R.C.M. loss of approximately 40 per cent.

†Average transfusion was 1,600 ml. These are transfusions given before analyses were performed.

‡Bleeding esophageal varices in 7.

Table III. *Clinical description of 20 patients with surgical oozing*

Patient No.	*Sex*	*Age*	*Diagnosis*	*Operation*	*Blood received before analysis (ml.)**	*Oozing first noted*	*Time of analysis*	*Oozing controlled*
1	F	50	Obstructive jaundice	Cholecystostomy	None	Postoperatively	Postoperatively	1 day postoperatively
2	F	22	Cirrhosis	Common bile duct exploration	500	At operation	At operation	At operation
3	M	24	Carcinoma, cecum	Laparotomy	500	At operation	Postoperatively	Postoperatively
4	F	23	Tuberculosis	Lobectomy	2,000	At operation	At operation	Postoperatively
5	M	42	Appendicitis	Appendectomy	2,000	Postoperatively	2 days postoperatively	2 days postoperatively
6	F	58	Gastric ulcer	Subtotal gastrectomy	2,500	At operation	1 day postoperatively	1 day postoperatively
7	F	13	Scoliosis	Spine fusion	2,500	At operation	Postoperatively	Postoperatively
8	F	43	Tuberculosis	Thoracoplasty	4,000	At operation	Postoperatively	1 day postoperatively
9	M	75	Mesenteric thrombosis	Small bowel resection	4,000	Postoperatively	2 days postoperatively	2 days postoperatively
10	M	34	Pancreatitis	Cholecystectomy	4,500	Postoperatively	1 day postoperatively	1 day postoperatively, died 2 days postoperatively
11	F	39	Stomal ulcer	Subtotal gastrectomy	5,000	At operation	2 days postoperatively	3 days postoperatively
12	F	55	Tuberculosis	Pneumonectomy	5,500	Postoperatively	1 day postoperatively	1 day postoperatively
13	F	24	Peptic ulcer	Gastrectomy, repair hepatic vein laceration	6,000	At operation	At operation	1 day postoperatively
14	M	32	Tuberculosis	Pneumonectomy	8,000	At operation	Postoperatively	Postoperatively
15	M	72	Carcinoma, pancreas	Pancreatectomy	8,500	Postoperatively	1 day postoperatively	1 day postoperatively
16	M	20	Cirrhosis	Portacaval shunt	9,500	At operation	2 days postoperatively	2 days postoperatively
17	M	62	Carcinoma, rectum	Attempted resection, colostomy	11,000	At operation	Postoperatively	Died postoperatively, still oozing

Table III—*Cont'd*

Patient No.	*Sex*	*Age*	*Diagnosis*	*Operation*	*Blood received before analysis (ml.)**	*Oozing first noted*	*Time of analysis*	*Oozing controlled*
18	F	51	Cirrhosis	Portacaval shunt	11,500	At operation	Postoperatively	Died 3 days postoperatively, oozing
19	F	43	Ruptured aortic aneurysm	Resection, aneurysm	12,000	At operation	Postoperatively	Postoperatively, died
20	M	35	Pancreatitis	Pancreatectomy	12,000	Postoperatively	Postoperatively	2 days postoperatively, died 3 days postoperatively

*Most of the patients received additional blood before the end of the oozing episode.

Table IV. *Abnormal coagulation measurements in patients with gastrointestinal bleeding*

Coagulation measurements	*Benign lesions*		*Malignant lesions*		*Associated hepatic disease*	
	*No. of tests**	*% of tests abnormal*	*No. of tests*	*% of tests abnormal*	*No. of tests*	*% of tests abnormal*
Vascular						
Bleeding time	103	3	17	6	11	18
Tourniquet test	99	1	17	12	11	0
Phase I						
Prothrombin consumption	52	16†	9	22†	10	40†
Clotting time	110	4	19	0	14	7
Clot retraction	109	5	19	5	14	14
Platelet smear	53	4	9	11	11	18
Factor V	100	4	18	0	8	38
Factor VII	100	2	18	11	8	13
Phase II						
Prothrombin activity	107	12†	19	16†	14	71†
Phase III						
Fibrinogen	50	6	6	0	11	27
Fibrinolysis	108	1	19	5	14	14
Average		5		8		22

*Each patient was tested once only.

†Two most frequently abnormal tests in each group.

were abnormal in the 10 patients who received more than 5,000 ml. of blood. This represents a significant increase in the number of abnormal measurements with increasing blood loss.

The distribution of the 60 abnormal values among the 11 determinations is summarized in Table VI.

Prothrombin activity, abnormal in the greatest number of patients with oozing (65 per cent), is followed by prothrombin consumption (55 per cent), bleeding time (50 per cent), and clot retraction (45 per cent). The other 7 values were abnormal in a smaller number of patients. They ranged from factor V (38 per cent) and fibrinogen (25 per cent) to tourniquet test (22 per cent), platelet smear (15 per cent), clotting time and fibrinolysis (10 per cent each), and finally factor VII (8 per cent).

Table V. *Occurrence of abnormal coagulation measurements in patients with surgical oozing*

	Vascular		*Phase I*		
Patient No.	*Bleeding time (min.)**	*Tourniquet test†*	*Prothrombin consumption (%)*	*Clotting time, 3rd tube (min.)*	*Clot retraction*
1	—	—	53§	10:00	Good
2	—	—	90	9:00	Good
3	3:30	Negative	over 90	6:00	Good
4	—	—	89	6:00	Good
5	over 10:00§	Negative	over 90	8:00	Good
6	2:30	Negative	over 90	5:00	Fair§
7	8:00§	Negative	87	3:30	Good
8	—	—	89	6:00	Good
9	over 15:00§	Negative	88	8:00	Good
10	4:00	—	82§	6:00	Fair§
11	13:00§	Positive§	72§	9:30	Good
12	9:00§	Negative	79§	8:30	Fair§
13	4:00	—	64§	11:00§	Poor§
14	over 10:00§	Negative	80§	29:00§	Poor§
15	3:00	—	37§	7:00	Fair§
16	4:00	—	80§	6:30	Fair§
17	—	—	79§	9:00	Good
18	6:00§	—	74§	6:00	Fair§
19	—	—	66§	7:30	Good
20	5:00	Positive§	over 90	7:30	Poor§

*Duke method for Patients 10, 13, 18.

†Ten petechiae (Patient 11), and 30 petechiae (Patient 20) in area of dime in antecubital fossa.

‡Rosenberg method for Patients 5, 7, 9, 11, 13, 14, 18, 20.

§Abnormal values. Sixty out of 189 (32 per cent).

COMMENT

The severity of the abnormal values in the patients with gastrointestinal bleeding extended from very mild to severe, with no particular pattern obvious. There was no correlation with severity of hemorrhage or diagnosis. Values for the 2 most frequently abnormal determinations are illustrative. Abnormal prothrombin consumptions, with the exception of one 39 per cent value, ranged from 70 to 84 per cent (average 77 per cent). Abnormal prothrombin activities ranged from 10 to 64 per cent (average 43 per cent).

One-half of the decreased prothrombin consumptions in the patients with gastrointestinal bleeding were due to defects in unspecified phase I factors, and the remainder were caused in equal numbers by platelet and factor V deficiency.

The specific causes for decreased prothrombin activities in these patients cannot be evaluated precisely because of incomplete data concerning factors V and VII. However, the available measurements indicate that deficiencies in factor V or VII are at least as frequent a cause for decreased prothrombin activities as is prothrombin deficiency.

It seems justifiable to conclude that there is no representative or serious coagulation defect which aggravates bleeding in the usual patient with gastrointestinal hemorrhage without significant liver disease or obvious hemorrhagic diathesis. There is no clinical evidence that coagulation was impaired in this group of patients.

The data on the patients with hepatic disease agree with the known high incidence of abnormal coagulation in patients of this type. It is possible that many of the patients studied bled unusually severely because of the coagulation abnormality present.

Our data indicate that there are 2 measurements, prothrombin activity and prothrombin consumption, which gave abnormal

			Phase II	*Phase III*	
Platelet smear	*Factor V deficiency*	*Factor VII deficiency*	*Prothrombin activity (%)*	*Fibrinogen (mg. %)‡*	*Fibrinolysis*
Adequate	No	No	100	397	Negative
Adequate	No	No	70	356	Negative
Adequate	Yes§	No	59§	468	Negative
Adequate	No	No	85	298	Clot lysis 24 hr.§
Adequate	—	—	57§	over 200	Negative
Adequate	No	No	78	498	Negative
Adequate	No	No	72	over 200	Negative
Adequate	No	Yes§	59§	274	Negative
Adequate	Yes§	No	59§	over 200	Negative
Adequate	—	—	53§	288	Negative
Adequate	—	—	55§	over 200	Negative
Adequate	Yes§	No	57§	150§	Negative
Adequate	Yes§	No	27§	150§	Negative
Adequate	—	—	23§	over 200	Negative
Less than 1/h.p.f.§	No	No	79	248	Negative
None on smear§	No	No	68	302	Negative
Adequate	—	—	39§	164§	Clot lysis 90 min.§
None on smear§	—	—	53§	150§	Negative
Adequate	Yes§	No	35§	151§	Negative
Adequate	—	—	10§	over 200	Negative

results more often than any other tests in the patients studied. These 2 tests appear to be the most useful ones for screening patients with gastrointestinal bleeding for possible coagulation defects.

Abnormalities in coagulation may be more frequent in patients in shock than in those who do not exhibit signs of clinical shock. Studies of hemorrhagic shock in animals suggest that early in shock (first hour) coagulation is accelerated but that as shock continues deficiencies in coagulation occur.[37, 42]

The existence of a large number of abnormal values in the patients with oozing lends strong support to the belief that coagulation difficulties are the important element in the oozing phenomenon. The severity of the abnormalities extends over a wide range, from seemingly mild to severe. The severely abnormal values could be suspected of contributing to the oozing. It is also conceivable that some of the milder aberrations may render coagulability ineffective to prevent hemorrhage in cases of extensive surgical procedures. In the case of fibrinogen it has been suggested that levels of approximately 150 mg. per cent are not adequate to control the bleeding in patients with surgical oozing.[31]

It would be useful to know if the coagulation defects seen in the oozing patients are present at the start of oozing or if they appear later as a result of increasing blood loss or transfusions. The fact that there are more abnormal measurements in the patients with the greatest amount of transfusion does not unequivocally answer this question. Only by more frequent analytical determinations on each patient could the time of onset of coagulation disturbance be determined.

Several of the values are abnormal in a large number of patients, and these can be considered as the most useful tests for patients with surgical oozing. However, it is important to ponder that even the most frequently abnormal determination, prothrombin activity, is within normal limits in 7 of 20 patients

Table VI. *Distribution of individual abnormal coagulation values in patients with surgical oozing*

Coagulation measurements (20 patients)	*No. of tests**	*% of tests abnormal*
Vascular		
Bleeding time	14	50
Tourniquet test	9	22
Phase I		
Prothrombin consumption	20	55
Clotting time	20	10
Clot retraction	20	45
Platelet smear	20	15
Factor V deficiency	13	38
Factor VII deficiency	13	8
Phase II		
Prothrombin activity	20	65
Phase III		
Fibrinogen	20	25
Fibrinolysis	20	10

*Each patient was tested once only.

Table VII. *The interpretation of abnormal coagulation values as specific coagulation defects in patients with surgical oozing*

Coagulation defects (20 patients)	*No. of patients tested*	*% of patients with defects*
1. Vascular	14	50
2. Clot retraction (unknown cause)	20	25
3. Antihemophilic globulin, plasma thromboplastic component, or others in phase I	20	25
4. Platelets	20	15
5. Factor V	13	38
6. Factor VII	13	8
7. Prothrombin or combined prothrombin factors	20	35
8. Fibrinogen	20	20
9. Fibrinolysis	20	10

with oozing (35 per cent). Thus, there is no single abnormal measurement which is characteristic of the 20 patients with surgical oozing.

A consideration of abnormal measurements without an understanding of the causative defects has only limited value. It is a knowledge of the underlying defect which has etiological and therapeutic importance.

The 60 abnormal coagulation measurements found in the patients with surgical oozing (Tables V and VI) have been interpreted in terms of 9 coagulation defects (Table VII). Interpretations are made within the limitations imposed by an analytical scheme of limited scope, and by current knowledge of the coagulation mechanism:

1. Vascular defect: Abnormal bleeding time or tourniquet test not related to platelet deficiency.
2. Clot retraction defect (unknown cause): Impaired clot retraction not due to platelet deficiency or elevated fibrinogen level.
3. Defect in antihemophilic globulin, plasma thromboplastic component, or others in phase I: Insufficient prothrombin consumption or prolonged clotting time, but adequate platelets and normal factor V.
4. Platelet defect.
5. Factor V defect.
6. Factor VII defect.
7. Prothrombin or combined prothrombin factors defect: Decreased prothrombin activity not correctable by prothrombin-free plasma or normal serum. The defect may be in prothrombin, in prothrombin plus factors V and/or VII, or in factors V plus VII.
8. Fibrinogen defect: Not due to demonstrable fibrinolysis. Elevated levels are not considered a defect.
9. Fibrinolysis defect.

Defects found in the greatest number of patients were the vascular defect, the factor V defect, and the prothrombin or combined prothrombin factors defect. Defects in the vascular component have not been cited previously as occurring in a significant number of cases of oozing during operation. This experience emphasizes the necessity of considering this factor. The other 6 defects are of less importance to the group as a whole, although in individual cases they may have been the chief cause of oozing. The inability to demonstrate rapid clot lysis in all but 1 instance should, according to Stefanini and Dameshek,[39] eliminate fibrinolysis as a major defect causing bleeding at the time of the analyses in this group of cases. However, fibrinolysis has been characterized as being rapidly transitory[45] and may have been missed in some of the patients. Four patients who were shown to have low fibrinogen

levels (about 150 mg. per cent) suggest this possibility. Fibrinolysis has been considered to be significant in some previous studies, although more recently it has not been given as much emphasis.

The single most frequently occurring defect, the vascular defect, is not present in 7 out of 14 patients with oozing (50 per cent), which indicates that there is no single coagulation defect which is characteristically present in these 20 patients with surgical oozing. Lack of a characteristic defect (or measurement) emphasizes the importance of detailed coagulation study of individual patients.

Occurrence of multiple coagulation defects (2 or more defects being considered multiple) is summarized in Table VIII. A positive correlation of multiple defects with clinical oozing has been made previously.[45] However, the occurrence of multiple coagulation defects is not characteristic of these 20 patients with oozing since 9 of them (45 per cent) have single defects or no defects.

Occurrence of multiple coagulation abnormalities in these patients serves to emphasize the usefulness of fresh whole blood and fresh frozen plasma in therapy. When laboratory facilities are unavailable, fresh blood or plasma is indicated because they contain most of the necessary coagulation factors. Often the usual tests show multiple abnormalities with no single striking defect, and again fresh blood or plasma is most important.

Table VIII. *Occurrence of multiple* coagulation defects in patients with surgical oozing*

No. of defects per patient	*No. of patients*
None	2†
1	7
2	3
3	6
4	2

*Two or more defects were considered multiple.

†Patients 2 and 6. The fair clot retraction in Patient 6 is considered to be a reflection of the elevated fibrinogen level.

SUMMARY

1. The coagulation mechanism of 163 patients with surgical bleeding was studied by means of 11 tests which reflect vascular integrity and all phases of blood coagulation.

2. In 143 patients with gastrointestinal bleeding the hemorrhage had resulted in an average estimated blood loss of 45 per cent of normal red blood cell mass. Patients with benign lesions had very few coagulation abnormalities, and patients with malignant lesions had only slightly more abnormal measurements. However, hepatic disease was associated with major coagulation disturbances. Two of the 11 tests, prothrombin activity and prothrombin consumption, were most frequently abnormal. They are the most useful for screening patients with gastrointestinal bleeding for coagulation defects.

3. Twenty patients were surgical patients who oozed excessively during operation or immediately thereafter. A high percentage of the coagulation measurements (32 per cent) during these bleeding episodes were abnormal. Those most frequently abnormal were prothrombin activity (abnormal in 65 per cent of patients), prothrombin consumption (abnormal in 55 per cent), and bleeding time (abnormal in 50 per cent). These are the most useful tests for the etiological diagnosis of patients with surgical oozing.

4. When the abnormal coagulation measurements were interpreted in terms of more specific coagulation defects, those most frequently present were a vascular defect, a factor V defect, and a defect in prothrombin or combined prothrombin factors. These defects were those most likely related to the oozing in the 20 patients.

5. Despite the large number of abnormal measurements and coagulation defects found in the patients with surgical oozing, there was no single one which was characteristic. The presence of multiple defects, present in 55 per cent of the patients, was likewise not characteristic. The need for assay of coagulation factors of individual patients is therefore indicated. Therapeutic use of fresh blood or plasma, because they contain most of the necessary constituents for coagulation, is also emphasized.

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Evaluation of the dissolution effect of fibrinolysin (plasmin) on induced vascular microthrombi

W. H. LEE, JR., M.D.
R. R. BRADHAM, M.D.
B. THREAT, B.A.
C. DAVENPORT, B.A.
LOS ANGELES, CALIF., AND CHARLESTON, S. C.
From the Departments of Surgery, University of California Medical Center and the Medical College of South Carolina

The development of a relatively purified, standardized preparation of human fibrinolysin† has caused a recent flurry of investigation, notably clinical and laboratory evaluation of the efficacy of this material in dissolving clots. The results of these investigations at the time of this writing are conflicting. Some of the reasons for the conflict in data concerning the assessment of fibrinolysin are apparent upon review of the available literature.

One problem has been the variance in the experimental methods of producing a clot in vivo. Some methods produced trauma to vascular endothelium and would theoretically perpetuate the tendency for thrombosis. Examples of these methods are the injection of chemical irritants into a vein, production of thrombosis by the passage of an electrical current through the wall of a vessel, direct crushing of a vessel between hemostats, and so forth. Other methods which have been used to stimulate thrombosis did not produce obvious trauma to the endothelium. Examples of these methods include the injection of thrombin into an isolated segment of vein and the production of complete stasis in a segment of vein by temporary "atraumatic" ligatures. Methods which produce venous thrombosis without overt trauma to the vascular endothelium may be analogous to clinical studies concerning phlebothrombosis, whereas methods which do produce trauma to the vascular endothelium may be more analogous to the clinical investigation of thrombophlebitis. The difficulty of evaluating the degree of inflammatory element in clinical venous thrombosis is a possible cause of the conflict in data from clinical studies regarding the evaluation of fibrinolysin therapy.

A second factor in the conflict of available data has been the tendency for investigators to utilize an indirect approach in attempting to measure the ability of fibrinolysin to dissolve a clot in vivo. Suggestive evidence, however strong, lacks definitive demonstration of clot dissolution in the living organism.

A third factor has been a considerable variance in the dosage of drugs employed, and the apparent difference in activity of 2 different commercially available preparations of fibrinolysin.[5] A fourth variable frequently controlled inadequately (as to dosage and individual tolerance) has been the concomitant use of anticoagulants (heparin).

A previous report[1] attempted to assess the efficacy of one preparation of fibrinolysin* by a method which employed a "trau-

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*Actase, fibrinolysin supplied by Ortho Research Foundation, Raritan, N. J.

matic" but standard venous clotting technique and evaluation of the result by direct observation of the clot. However, the experimental control in this series of experiments depended upon the use of the contralateral femoral vein in the dog as the "control" to establish evidence of thrombosis. In addition, the possibility of partial dissolution of clots with occult embolization into the systemic venous circulation (simulating clot lysis) could not be assessed. The present study was therefore undertaken in order to evaluate directly the ability of fibrinolysin to dissolve an arterial microthrombus in vivo, with control of the experimental variables mentioned.

METHOD

Microscopic observations were made in vivo on the effect of fibrinolysin on thrombosis produced in small mesenteric vessels (50 to 100 μ in diameter) of dogs. Mongrel dogs which weighed from 10 to 15 kilograms, were anesthetized intravenously with pentobarbital sodium and subjected to a midline laparotomy. A loop of small bowel with its mesentery was gently brought out and suspended over a porthole in a paraffinized balsa sheet mounted in a hood over the animal's abdomen (Fig. 1). The tissue was continuously moistened with sterile isotonic saline solution at room temperature, and the mesentery was transilluminated with a Knisely quartz-rod apparatus.[3] Observations of the circulation were then made in vivo with a standard binocular dissecting microscope mounted appropriately on a heavy floor stand. Good resolution up to 90 diameters magnification was possible with this instrument.

Series 1. In a group of 5 dogs, thrombosis was produced in the selected segments of artery and vein by application of a copper microelectrode to the vessels which delivered a 12 v. direct current over a 2- to 5-second period. Duration of the current was determined by the interval necessary to produce complete stasis and agglutination of the blood in the vessel segment. A localized thrombus was uniformly produced without visible microscopic evidence of tissue injury, except a slight degree of turbidity in the alveolar tissue adjacent to the vessels. Fibrinolysin was infused intravenously over a 1-hour period in doses varying from 50,000 to 250,000 units* in 250 ml. of isotonic saline solution. Observations were continued for 3 hours after the infusion was completed.

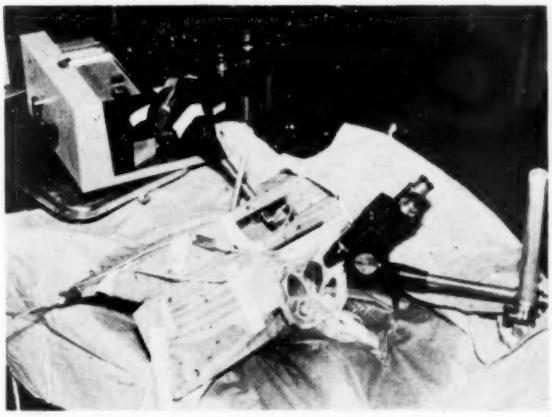

Fig. 1. The transillumination apparatus can be simple. Light source here is a standard 500 w. slide projector, and all other parts except the quartz rod are standard laboratory equipment. A later model is more compact, sophisticated, and expensive.

Series 2. Thrombosis was produced as in the first series. A control solution of 250 ml. of isotonic saline was directly perfused into a branch of the mesenteric artery (by cannulation) supplying the clotted segment over a 2-hour period in 10 dogs.

Series 3. In 11 dogs thrombosis was produced as in Series 1. Doses of fibrinolysin which varied from 300,000 to 1 million units in 250 ml. of 5 per cent dextrose in distilled water were directly perfused into the mesenteric artery branch supplying the thrombosed segment as before. Observations were continued for 3 hours after the perfusion.

Series 4. In 5 dogs no electrical current was used. Thrombosis was produced by injection of a suspension of ground, preformed clot through the intra-arterial cannula into the mesenteric artery vasculature. A clot was formed by withdrawing 2 ml. of blood from the dog and allowing it to clot

*Units as defined by the Ortho Pharmaceutical Corporation for the Actase preparation.

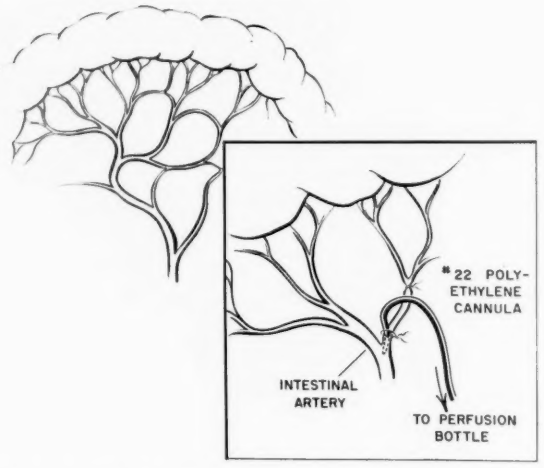

Fig. 2. The arterial branch was cannulated through a side limb of a bifurcation to avoid occlusion of the blood flow to the area under study.

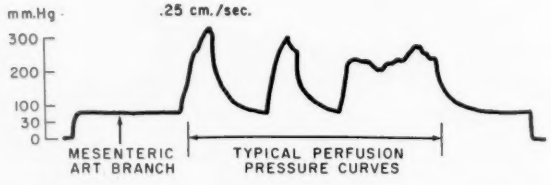

Fig. 3. Pressure of perfusion was intermittent. Each cycle lasted 5 to 6 seconds, and reached a peak of approximately 300 mm. Hg.

in a test tube, then adding 3 ml. of isotonic saline solution to the clot and mixing this vigorously with a blunt glass rod. The fragmented, suspended clot was infused through a 22 gauge polyethylene cannula at a transient perfusion pressure of approximately 325 mm. Hg into one proximal limb of a bifurcation of an intestinal artery (Fig. 2). This invariably produced embolization of the other limb of the bifurcation. The route of the embolus was charted by adding 1 to 2 drops of fluorescein to the clot suspension. After the production of thrombosis in this fashion, a control solution of 200 ml. of sterile isotonic saline was perfused into the arterial cannula by intermittent positive pressure ranging from 75 to 300 mm. Hg with a mean perfusion pressure of 160 mm. Hg (Fig. 3). After this control perfusion into the thrombosed area, a solution of 250 ml. of 5 per cent dextrose in water containing 300,000 units of fibrinolysin was perfused into the thrombosed segments of the vessels at a similar perfusion pressure. Three of the 5 dogs were heparinized by the intravenous administration of 3 mg. per kilogram of heparin sodium as the perfusion was begun.

RESULTS

There was no dissolution of the thrombi in the 5 dogs which received fibrinolysin intravenously in Series 1.

Neither was there any dissolution or flushing of the thrombi produced by electrical current in the dogs which received saline control perfusions intra-arterially in Series 2.

An interesting sequence of events followed the initiation of thrombosis and subsequent intra-arterial infusion of fibrinolysin in 8 of the 11 dogs of Series 3. The electrical stimulus produced complete agglutination of the blood in the vessels, which, prior to perfusion, was quickly replaced by a very sluggish flow of red blood cell aggregates (10 to 50 μ in diameter) and white clear aggregates believed to be composed of platelets and/or fibrin. These aggregates flowed in a progressively sluggish fashion over approximately a 10-minute period, and then were again replaced by complete agglutination and apparent thrombosis. The subsequent infusion of fibrinolysin resulted in alternate cycles of (1) incomplete dissolution, (2) complete agglutination, and then (3) partial dissolution, and so forth, with the red blood cell and white aggregates breaking off and flowing away from the agglutinated segmental masses. A sluggish flow in the thrombosed vessel would resume, only to be followed again by agglutination. When the fibrinolysin infusion was completed, thrombosis recurred within 15 to 30 minutes and was persistent. Heparinization of 4 dogs in this series during perfusion produced no apparent change in the sequence or ultimate result. In the remaining 3 dogs, there was no demonstrable change in the clotted segment.

In dogs of Series 4, in which thrombosis was initiated with preformed, injected clots

to produce an experimental situation in which, theoretically, there was minimal or no vascular endothelial damage, the saline pressure perfusion failed to flush the thrombosed segments or to dissolve the clots. The fibrinolysin pressure perfusion resulted in the same sequence of events that was described for the 8 dogs of Series 3. Partial dissolution of the thrombi was apparently obtained, with flushing of agglutinated masses out of the larger vessels (from 100 μ up), but many smaller arterioles and venules in a range of size from 15 to 30 μ remained persistently clotted during the perfusion. The final picture after the perfusion was one of ultimate thrombosis, despite intravenous heparinization of 3 dogs with 3 mg. per kilogram of heparin sodium during the fibrinolysin perfusion.

DISCUSSION

In order for fibrinolysin to effectively dissolve thrombi in a living organism, 3 factors seem prerequisite. First, the material must possess a sufficiently potent fibrinolytic activity to dissolve the clot before it is itself destroyed by antifibrinolytic materials circulating in the blood of the living organism. Second, the fibrinolytic agent must be placed into the circulation of the organism in such a fashion that it is able to reach the clotted vessel segment and obtain a sufficient concentration in the plasmic fluid which bathes the clot and its fibrin framework. It seems from this that only vessels large enough to possess vasa vasorum could be treated by fibrinolytic dissolution of the thrombi. However, ancillary experiments in this laboratory have demonstrated that the material perfused as in Series 3 and Series 4 reached the interior of the lumens of thrombosed vessels as evidenced by the rapid appearance of perfused fluorescein shown by transilluminated ultraviolet light inside the vessels. Third, effective dissolution of the thrombus should be considered complete dissolution of the thrombus. For example, if a venous thrombus is softened and partially fragmented, it may be swept away from the vessel which it occludes and continue in the systemic venous circulation as unsuspected multiple smaller emboli which may or may not lodge in vessels of circulatory importance, depending upon the size of the clot fragments. In an artery, however, should a clot be incompletely dissolved, the fragments would be swept downstream into a progressively narrowing truncated cone (for such is the physical nature of the shape of arterial vessels[4]), and ultimately occlude many smaller branches of the arteriolar or capillary circulation, depending upon the size of the fragments.

The development of available fibrinolysin preparations represents a significant step toward a successful chemotherapeutic attack upon acute vascular thromboembolic disease. However, the clinical application of this chemotherapeutic concept is limited at the present time by the relative impurity or impotency of the fibrinolysin preparation. A possible exception is the use of fibrinolysin preparation as a chemotherapeutic adjunct to some primarily surgical therapeutic measure, such as arterial thrombectomy with fibrinolysin flushing, or removal of peripheral emboli by retrograde flushing procedures such as have been previously described by Crawford.[2] It is possible and, indeed, probable that the efficiency of such a flush procedure may well be enhanced by the employment of fibrinolysin in the irrigant fluid.

SUMMARY AND CONCLUSIONS

From the experiments presented and the data available in the literature, the authors have concluded that the fibrinolysin preparation used in these experiments does possess fibrinolytic activity in vivo. This activity, however, is insufficient to dissolve experimental thrombi completely, and in experimental animals venous clots are apparently softened or partially fragmented[1] and swept off in the systemic circulation in the form of multiple emboli, either in liver or lung, depending upon the experimental conditions. (The latter hypothesis is unproved.) In the case of arterial thrombi, the clot is apparently softened and partially lysed, and is

swept forward to embolize arteriolar or capillary beds distal to the thrombosed segment. A progressive stasis of blood flow in the total vascular beds supplied by the thrombosed vessel occurs until a point of complete stasis in the vascular bed supplied by this vessel is reached. This ultimately results in recurrent and persistent thrombosis after the perfusion of fibrinolysin.

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An attempt at development of agammaglobulinemia in adult rats by treatment with an extract of the fetal thymus

JEREMI CZAPLICKI
ZABRZE, POLAND
From the Department of Histology and Embryology, Silesian Academy of Medicine

In animals, intrafetal treatment with an albumin of another individual prevents the recipient from displaying immunologic reactions to the albumin of the donor after birth for a prolonged or permanent period. This phenomenon has been called "acquired tolerance," and the fetal period during which it occurs the "period of tolerance."

To explain tolerance, it has been postulated that a previously unknown hormone arises in the fetal thymus. This idea occurred to me by association of the anergy of fetal life with the condition of status thymicus or lymphatism which arises after birth. I found support of this concept a few years ago in the description by MacLean and associates[1] of agammaglobulinemia and anergy which was observed in a 55-year-old man suffering from a thymic tumor. It is possible that this thymic tumor had caused a functional regression of the thymus back to the fetal state in which the thymus produces the hypothetical hormone.

In order to test the hypothesis, the effect of extracts of the fetal thymus of pigs on the serum gamma globulins of rats was studied. Although these investigations are not yet complete, the preliminary results seem to me to justify this early communication.

Revised by Dr. Richard C. Lillehei, University of Minnesota Medical Center, Minneapolis, Minn.

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METHODS AND RESULTS

Nine adult rats have been used in this study so far. The first studies were carried out on 4 of the rats. The first rat was treated subcutaneously with an extract prepared from the thymus of fetal pigs obtained in the first half of fetal life. The second rat was treated in a similar manner. The third was treated with a similarly prepared thymic extract which previously had been frozen. The fourth rat was treated as the first 2, with the exception that the thymus was taken from pigs obtained during the last half of fetal life. The rats were treated thrice weekly for 2 weeks. Five days after the final treatment, the rats were bled out and a blotting-paper electrophoresis of the serum obtained.

The serum gammaglobulin levels in the first 3 rats were low, while in the fourth rat the level was fairly high (Table I).

In the second group of experiments carried out on 3 rats, the first rat was given an extract of the thymus of pigs obtained in the first half of fetal life. The second rat was administered a liver extract from the same fetal pig which was of the same weight and quantity as the thymic extract. The third rat was treated with a splenic extract of the same fetal pig, and again this extract was of the same weight and quantity as the thymic extract. Control blood specimens

Table I

Rat No.	*Albumin (%)*	*Globulin*		
		$\alpha_1 + \alpha_2$ *(%)*	$\beta_1 + \beta_2$ *(%)*	γ *(%)*
1	36.2	22.2	22.8	17.0
2	38.0	22.4	21.4	20.0
3	37.7	21.9	20.8	19.6
4	21.5	19.0	21.9	37.6

were obtained from the tail veins of the rats before the start of the injections and again a fortnight after treatment with the various extracts had started. These blood samples were used for blood morphologic studies, total albumin determinations, and blotting-paper electrophoresis of the serum. The results of this second group of experiments are seen in Table II.

Table II

Rat No.	*Protein (Gm. %)*		*Albumin (%)*		*Globulin*						*Erythrocytes (million)*		*Leukocytes*	
					$\alpha_1 + \alpha_2$ *(%)*		$\beta_1 + \beta_2$ *(%)*		γ *(%)*					
	Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	7.8	8.2	27.0	27.4	25.5	19.6	23.0	27.0	24.5	26.0	6.9	3.2	11,000	12,000
2	7.9	14.0	33.3	18.5	23.8	13.5	22.7	15.0	27.2	53.0	5.7	17.0	14,000	19,500
3	7.8	17.0	27.2	13.1	23.2	13.1	22.9	12.8	26.7	61.0	7.2	13.4	10,000	21,000

Table III

	Before experiment	*During experiment*			*After experiment*				
		After 1 wk.	*After 2 wk.*	*After 3 wk.*	*After 1 wk.*	*After 2 wk.*	*After 3 wk.*	*After 4 wk.*	*After 5 wk.*
Rat No. 1									
Protein (mg./100 ml.)	7.8	9.6	8.4	8.4	7.9	7.9	7.8	7.8	
Albumin (%)	26.3	20.5	29	27.2	32.6	28.6	24.1	27.4	
α Globulin (%)	26.4	16.7	22.1	20.2	35.5	32.5	22.9	19.7	
β Globulin (%)	22.9	21.2	16.8	20.2	31.9	38.9	53	27	
γ Globulin (%)	24.4	41.6	32.1	32.4	—	—	—	25.9	
Erythrocytes (million)	7.64	7.97	4.56	4.85	5.37	6.12	5.74	6.01	
Hemoglobin (%)	140	143	99	97	75	73	74	81	
Index Hb	0.8	0.9	1.1	1	0.7	0.6	0.6	0.7	
Leukocytes	16,000	12,000	13,000	12,000	14,200	11,900	13,400	14,100	
Methamyelocytes (%)	—	5	4	1	2	3	1	4	
Nonfilamented cells (%)	—	1	3	—	—	—	—	1	
Segmented cells (%)	27	23	25	34	17	24	30	23	
Lymphocytes (%)	71	71	67	65	80	73	69	72	
Eosinophils (%)	1	—	1	—	1	—	—	—	
Monocytes (%)	1	—	—	—	—	—	—	—	
Rat No. 2									
Protein (mg./100 ml.)	7.8	9.5	9.5	8	7.8	7.9		7.9	7.7
Albumin (%)	32.5	31.6	29.6	30.4	30.4	29.6		25.1	28.4
α Globulin (%)	22.8	22.9	23.4	22.7	37.8	31.5		24.9	18.7
β Globulin (%)	22.5	27.5	30.9	29	31.8	38.9		50	29.7
γ Globulin (%)	22.2	15.4	16.1	17.9	—	—		—	23.2
Erythrocytes (million)	5.22	4.3	3.74	3.88	5.29	5.4		5.75	6.42
Hemoglobin (%)	82	73	67	69	76	75		74	90
Index Hb	0.7	0.6	0.9	0.9	0.7	0.7		0.6	0.7
Leukocytes	10,100	16,900	8,900	12,800	12,700	13,400		14,100	18,600
Methamyelocytes (%)	6	7	3	3	2	2		4	6
Nonfilamented cells (%)	—	—	—	—	1	—		1	1
Segmented cells (%)	20	20	20	31	17	19		15	21
Lymphocytes (%)	72	73	77	64	80	89		80	72
Eosinophils (%)	1	—	—	2	—	—		—	—
Monocytes (%)	1	—	—	—	—	—		—	—

In the final phase of the experiment, 2 rats were injected intraperitoneally with extract prepared from the thymus of pigs obtained in the first half of fetal life. Morphologic blood analyses and blotting-paper electrophoreses were carried out every week for 2 months. During the period of injections, changes were observed which resembled those in the experiments described. One week after the injections had been stopped, complete agammaglobulinemia occurred which lasted 3 weeks in 1 rat and 4 weeks in the other. These results, as well as erythrocyte counts and hemoglobin indices of the 2 rats in this experiment, are seen in Table III.

SUMMARY AND CONCLUSIONS

These experiments suggest that the fetal thymus may produce a substance or hormone which inhibits the production of gamma globulins. In the publications at my disposal, no mention of the possibility of achieving total agammaglobulinemia by biologic means has been noted. If the proposed hormone in question can be isolated, this may lead to the achievement of acquired tolerance in postfetal life and to a solution to the problem of organ transplants.

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Contribution of functional ablation of the pyloroantral mechanism to malabsorption in gastrectomized dogs

PAUL H. JORDAN, JR., M.D.
GAINESVILLE, FLA., AND LOS ANGELES, CALIF.
From the Department of Surgery, University of Florida, and the Los Angeles Veterans Administration Hospital

An increased fecal excretion of fat and protein is a frequent occurrence after operative procedures upon the stomach for treatment of peptic ulcer or gastric carcinoma. Everson[2] has drawn attention to several factors possibly responsible for this phenomenon. Evidence exists that the malabsorption is due to multiple defects created by operation and is not the exclusive result of any one factor.

Ablation or short circuiting of the pyloric sphincter and gastric antrum is common to all operative procedures upon the stomach except segmental resection performed without pyloroplasty. Studies performed upon dogs indicate that the degree of malabsorption associated with the latter operation is less than with any other type of gastric resection.[1] Since the pyloroantral pump, by its muscular action, appears to regulate the rhythmical evacuation of the stomach,[4] it was appropriate to evaluate the contribution made by the loss of this mechanism upon the absorption of fat and protein.

METHODS

Two groups of mongrel dogs were used and the experiment in each group was divided into 3 phases. Phase 1 in both groups consisted of a control period. The animals of Group I underwent a segmental gastric resection during Phase 2 and subsequently a Heineke-Mikulicz pyloroplasty during Phase 3. The control period in animals of Group II was followed by pyloroplasty during Phase 2 and segmental gastric resection in Phase 3. The animals were allowed a recovery period of 1 month after pyloroplasty and 2 months after gastric resection before studies were performed.

Six dogs in each group completed all phases of the study while 2 dogs in Group I and 1 dog in Group II completed only Phases 1 and 2. Not less than 3 consecutive 6-day metabolic balance studies were made on all dogs during the control periods and after recovery from the operations performed during Phases 2 and 3. In the case of Dog 3 in Group I, alterations in absorption were negligible at the completion of Phase 3. Pyloroplasty was performed, therefore, a second time to insure transection of all the antral musculature. Three additional metabolic periods were performed. Six 6-day metabolic periods were performed after gastric resection during Phase 3 upon Dogs, 4, 5, and 6 of Group II.

The diet during each metabolic period consisted of 80 calories per kilogram of body weight per day based upon the dog's original weight. This included 5 Gm. of protein and 4 Gm. of fat per kilogram. The diet, a commercial dog food supplemented with lard, was analyzed for its fat and protein content. All meals prepared were eaten; thus, no analysis of rejected meals was required.

Each 6-day stool collection was delineated

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by carmine markers. Each was homogenized and duplicate aliquots taken for fat and protein analyses which were repeated if they did not agree within 5 per cent. Fat determinations were by the Mojonnier extraction methods.[5] Proteins were measured by the micro-Kjeldahl method and expressed in grams of nitrogen. Because of the analytical accuracy and the meticulous care in the preparation of diets and the collection of stools, it was assumed that the error in the estimated fecal fat and nitrogen levels for any collection period was not greater than 10 per cent. This was equivalent to approximately 1 per cent of the ingested fat and 2 per cent of the ingested nitrogen. Consequently, changes in excretion were considered analytically significant if the differences between periods were in excess of 2 per cent and 4 per cent of the ingested fat and nitrogen, respectively.

The pyloroplasties were constructed by making longitudinal incisions that transected a major portion, if not all, of the musculature of the pylorus and which were extended for an equal distance into the duodenum. The incisions were closed transversely to effectively destroy the function of the pyloroantral pump without compromise of storage capacity. The segmental resections aimed at removal of 75 per cent of the stomach with retention of the cardia, the antrum, and the vagal fibers to the antrum. In order to verify the extent of resection, the mucosa of the resected portion of the stomach was stripped from its muscle and weighed. When the dog was subsequently sacrificed, the remaining mucosa was weighed and the per cent of resection calculated. In Group I the extent of resection ranged from 50 to 89 per cent. In animals of Group II the resection ranged from 48 to 62 per cent. In our opinion this method was not entirely reliable because much of the scar tissue associated with suture lines was included in the remaining mucosal specimen and resulted in underestimation of the magnitude of resection. The weight of mucosa initially removed was a more reliable index of the magnitude of resection and indicated that the gastrectomies were larger in Group I than in Group II.

RESULTS

Fat absorption. Four of the 8 dogs in Group I demonstrated significant increases in fat excretion after gastric resection. Subsequent pyloroplasty was performed upon 6 of the dogs in this group. The excretion of fat was significantly increased in 4 of these animals to an amount above that seen with gastrectomy alone. Comparison of the amounts of fat excreted during Phases 1 and 3 demonstrated that a significant increase in the fecal excretion resulted in 5 of 6 dogs which underwent both operations. The differences between the per cent of ingested fat excreted in the stool by animals of Group I during the 3 phases of this study are tabulated in Table I.

In Group II, fat excretion was significantly increased by pyloroplasty in 2 of 7 dogs. After gastric resection, fat excretion was increased in 5 of 6 dogs above that seen with pyloroplasty alone. The increase was significant in 2. The fecal fat level observed during Phase 3 was increased significantly in 4 dogs above that encountered during the control period (Table II).

Nitrogen absorption. All 8 dogs of Group I demonstrated an increased excretion of nitrogen after segmental resection. This increase was significant in 5. In 5 of the 6

Table I. *Differences in the per cent of ingested fat in stool during 3 phases of experiment in Group I*

Dog No.	*Sleeve gastric resection–control*	*(Sleeve gastric resection + pyloroplasty)–sleeve gastric resection*	*(Sleeve gastric resection + pyloroplasty)–control*
1	0.8	6.0	6.8
2	0.5	4.7	5.2
3	−1.1	1.3	0.2 (−0.3*)
4	3.0	1.2	4.2
5	2.0	5.8	7.8
6	8.6	3.4	12.0
7	5.2	—	—
8	−0.5	—	—

*From second series of metabolic studies performed during Phase 3.

Table II. *Differences in the per cent of ingested fat in stool during 3 phases of experiment in Group II*

Dog No.	*Pyloroplasty – control*	*(Pyloroplasty + sleeve gastric resection)– pyloroplasty*	*(Pyloroplasty + sleeve gastric resection)– control*
1	0.4	1.2	1.6
2	4.1	−1.8	2.3
3	1.4	1.8	3.2
4	0.6	0.2	0.8 (−0.2*)
5	0.5	6.3	6.8 (2.6*)
6	0.5	8.6	9.1 (8.9*)
7	2.8	—	—

*From second series of metabolic studies performed during Phase 3.

Table III. *Differences in the per cent of ingested nitrogen in stool during 3 phases of experiment on dogs in Group I*

Dog No.	*Sleeve gastric resection–control*	*(Sleeve gastric resection + pyloroplasty)–sleeve gastric resection*	*(Sleeve gastric resection + pyloroplasty)–control*
1	2.3	1.7	4.0
2	6.5	.0	6.5
3	1.7	3.0	4.7 (2.9*)
4	2.5	5.0	7.5
5	10.6	1.1	11.7
6	15.0	0.4	15.4
7	13.2	—	—
8	6.2	—	—

*From second series of metabolic studies performed during Phase 3.

Table IV. *Differences in the percent of ingested nitrogen in stool during 3 phases of experiment on dogs in Group II*

Dog No.	*Pyloroplasty–control*	*(Pyloroplasty + sleeve gastric resection)– pyloroplasty*	*(Pyloroplasty + sleeve gastric resection)–control*
1	3.5	4.8	8.3
2	1.6	9.7	11.3
3	5.7	4.5	10.2
4	−2.5	1.1	−1.4 (−3.3*)
5	1.6	−0.2	1.4 (2.2*)
6	0.4	4.8	5.2 (4.1*)
7	5.7	—	—

*From second series of metabolic studies performed during Phase 3.

dogs which underwent subsequent pyloroplasty, nitrogen excretion was increased above that seen with gastrectomy alone and in 1 the increase was significant. In all dogs the excretion of nitrogen observed during Phase 3 was significantly greater than that encountered during the control period. The differences in the per cent of ingested nitrogen excreted in the stool during the 3 phases are tabulated in Table III.

In Group II, nitrogen excretion was significantly increased after pyloroplasty in 2 of the 7 dogs. The addition of gastric resection in 6 dogs significantly increased nitrogen excretion in 4 above that seen with pyloroplasty alone. The fecal nitrogen level observed during Phase 3 was significantly increased in 4 dogs above that encountered during the control period (Table IV).

Ten of the 12 dogs which underwent combined operations in Groups I and II had increased excretion of nitrogen. In 5, this defect was solely attributable to the gastrectomy which was performed as the primary procedure in 3 dogs and the secondary procedure in 2. In 5 dogs, pyloroplasty and gastrectomy appeared equally responsible for the defect in nitrogen absorption. In no dog was the increased fecal nitrogen level attributable to pyloroplasty alone.

The average size of the actual gastrectomies was estimated at 75 per cent in dogs of Group I and 57 per cent in dogs of Group II. The average weight losses during the experiments were 0.6 and 0.2 Kg. in the 2 groups, respectively. It was not possible in this study to correlate the magnitude of gastrectomy with the degree of steatorrhea and azotorrhea. It was also not possible to correlate the amount of fat and nitrogen excreted with changes in body weight.

No time limit was placed upon the dogs for the consumption of their daily rations. It was an impression that the rate with which food was eaten exerted a significant effect upon the animals' nutritional status. This was particularly true for Dog 3 in Group I, which required over 12 hours to eat his daily rations. This dog exhibited nearly normal value for fat and nitrogen ex-

cretion during the 3 phases of study and body weight increased during the experiment. A second pyloroplasty in this animal failed to alter the weight or produce any degree of malabsorption.

DISCUSSION

The importance of the pyloric antrum for the control of gastric emptying was demonstrated by Quigley.[4] Work by Friesen[3] implied that the pylorus, by virtue of its regulation of gastric evacuation, exerts an important influence in the maintenance of body weight in the dog and prevention of the dumping syndrome in man. Everson[2] and others have stated that the loss of fecal fat and protein after segmental gastric resection is less than that which occurs after conventional resections. For these reasons the present study was expected to demonstrate that functional ablation of the pyloroantral pump is a significant factor responsible for malabsorption after gastrectomy. This hypothesis was substantiated; however, the effect was less than that which had been anticipated.

As the primary operation, pyloroplasty appeared to have little effect upon fat and protein absorption. When it was performed as the secondary operation after segmental gastrectomy, absorption of fat was significantly reduced, whereas the absorption of protein was minimally affected. Segmental gastrectomy, on the other hand, had a significant effect upon the absorption of fat and protein when it was performed either as a primary or secondary operation. The malabsorption of fat resulting from segmental resection performed as a secondary operation was not as great, however, as that associated with pyloroplasty performed as a secondary operation. It appears that the magnitude of the segmental resections performed upon dogs of Group II was less than that of the resections performed in Group I and may account for the over-all difference in the absorption of fat after combined operations in the 2 groups. That this is not the complete explanation is suggested by the fact that gastrectomy as the secondary operation in Group II exerted a greater effect upon nitrogen excretion than did pyloroplasty as the secondary operation in Group I. The difference in the effect of segmental gastric resection and pyloroplasty upon the absorption of fat and protein after combined operations suggests that loss of the pyloroantral pump exerts its greatest effect upon absorption of fat while the loss of the stomach's storage capacity exerts its greatest effect upon protein absorption.

SUMMARY

Conventional subtotal gastrectomy includes ablation of the pyloroantral pump and the storage capacity of the stomach. The effects exerted by the loss of these functions of the stomach upon absorption were evaluated independently and in combination during experimental studies on dogs.

The results suggest that loss of the storage capacity of the stomach exerted a greater effect upon postgastrectomy malabsorption than did interference with the pyloroantral pump. Disruption of the latter mechanism by pyloroplasty when accompanied by segmental gastric resection significantly increased the excretion of fat but had little effect upon excretion of protein. Pyloroplasty unaccompanied by gastrectomy had an insignificant effect upon fecal excretion of fat and protein.

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Clinical and experimental observations on heterotopic osseous formation in abdominal wall scars

KENNETH L. CLASSEN, M.D.
R. F. WIEDERANDERS, M.D.*
J. LYNWOOD HERRINGTON, JR., M.D.
NASHVILLE, TENN.
From the Surgical Service, Thayer Veterans Administration Hospital; Department of Surgery, Vanderbilt University School of Medicine; and the Edwards-Eve Clinic

The occurrence of heterotopic osseous formation in abdominal wall scars has long been regarded as a medical curiosity and represents one of Nature's perplexing whims. The relative infrequency of this clinical finding is evidenced by the paucity of reported cases in the literature.

In a recent report from this institution,[4] 10 clinical cases of bone formation which took place in abdominal wall scars were described. Since the previous publication, 20 additional cases have been discovered on our services. Thus, the present report represents a detailed analysis of the entire group of 30 cases and, in addition, experimental data on our attempts to produce bone growth in laparotomy scars of the experimental animal.

CLINICAL MATERIAL

The 30 cases of osseous formation in abdominal wall scars occurred entirely in patients of the male sex. The age range extended from 23 to 74 years and the average age at time of discovery of heterotopic bone formation was 56 years. Twelve of the 30 patients were in the seventh decade of life. Each of the patients had originally had a cleanly incised laparotomy which was meticulously closed with a continuous catgut suture for the peritoneum and either interrupted silk sutures, stainless steel wire, or chromic catgut for the fascial layers. The skin was closed routinely with silk.

Among the 30 patients, it is of interest that 23 had laparotomy incisions placed in the supraumbilical area, extending from the ensiform process or the costochondral arch superiorly to the umbilicus or periumbilical area inferiorly. The original operation in the group of 23 patients was vagotomy and gastric resection in 16 cases, repair of esophageal hiatal hernia in 2, resection for gastric carcinoma in 3, exploration for gunshot wound of the upper abdominal viscera in 1, and in 1 instance exploratory laparotomy without definitive intraperitoneal operation. Of the 7 remaining patients, 4 had incisions placed in the low paramedian area of the abdominal wall, while 3 underwent midline incisions extending from the ensiform process to the pubis. The indications for the original operation in this group were carcinoma of the left colon in 4 instances, abdominal aortic aneurysm in 2, and marginal ulcer after inadequate resection in 1. It is to be noted that 3 of the latter 7 incisions extended to or impinged on skeletal structures (Fig. 1). Four of the 30 patients developed postoperative wound infections of mild to moderate severity. In 26 cases the laparotomy wound healed without complications. There was no instance of postoperative hematoma formation, and none of the 4 infected wounds drained for any appreciable length of time (Fig. 2).

The first indication which suggested the

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*Present address: Department of Surgery, Veterans Administration Hospital, Omaha, Neb.

likelihood of early heterotopic bone formation during the postoperative period was the presence of persistent tenderness in the abdominal wall scar. As a general rule, most tenderness has disappeared in clean wounds after 14 days. In the cases under consideration, persistent and increasing tenderness in the absence of infection was the first sign of early osseous activity in the abdominal wall scar. This was noted in 18 of the 30 patients (60 per cent). Unusual tenderness occurred as early as 2 weeks postoperatively and up to as late as 6 months. As the heterotopic bone developed further, a major portion of the abdominal wall tenderness usually disappeared, as well as abdominal wall hyperesthesia. With further development of bone growth, the patients began to note a "stabbing" sensation in the abdominal wall, usually initiated by flexion of the abdominal wall musculature. The presence of an abdominal wall mass was usually then discovered, as a rule first by the patient and later by the physician. A mass was noted by 25 of the 30 patients (83 per cent). In the remaining 5 patients, a mass was first discovered by the physician on physical examination. Three patients in the group discovered the presence of a mass as early as 2 weeks after operation. In most instances within a few months after operation the mass had grown sufficiently in size to become palpable. In several cases the bone growths were of such length (7 to 15 cm.) as to restrict forward body bending and to limit physical activity. In 6 instances, actual fracture of the bone occurred during exercise. This interesting finding was first demonstrated by roentgen study as a rule, but later, upon careful questioning, the patient could usually recall the exact time and the physical event which resulted in the fracture. Several patients experienced a "grating" sound in the upper abdominal wall at the time of the fracture, after which they no longer experienced discomfort upon flexion of the abdominal wall musculature (Fig. 3).

Routine postoperative gastrointestinal barium studies and scout films of the abdomen were performed on the majority of the 30 patients from 4 to 8 weeks after operation. Approximately one-third of the group examined demonstrated evidence of radiodensity in the abdominal wall within 2

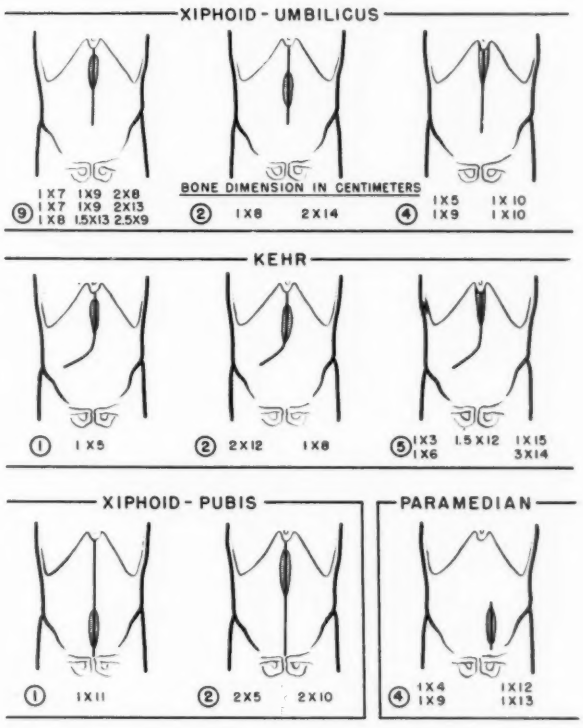


Fig. 1. Site and size of bone formation.

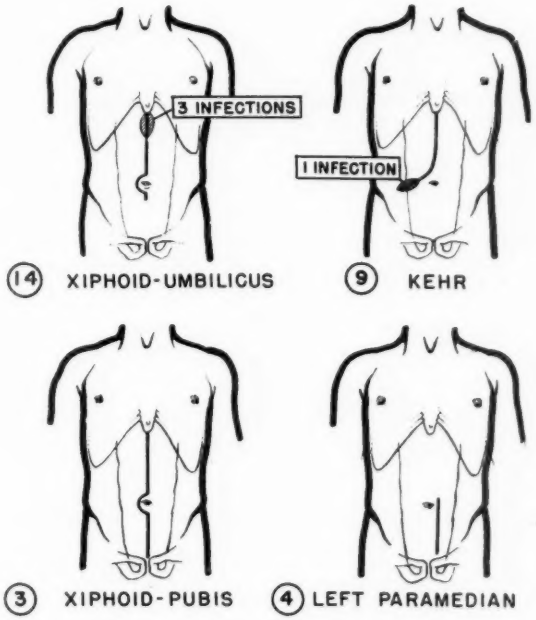
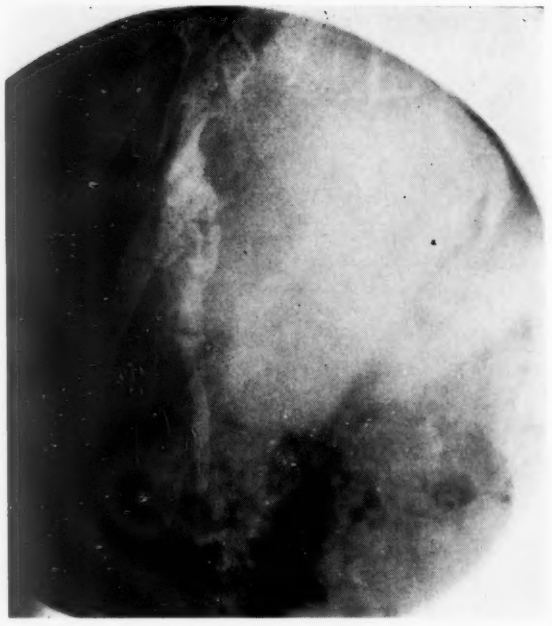


Fig. 2. Original incision.



A

B

Fig. 3. *A,* Lateral film shows the heterotopic osseous growth. A fracture in the midportion of the bone is demonstrated. (From SURGERY **47:** 918, 1960.) *B,* Excised specimen shows the ensiform process which has been sectioned. The heterotopic bone shows 2 distinct fracture sites.

months after the operative procedure. Presumably this radiodensity represented early deposition of calcium in the soft tissues about the laparotomy scar. This finding was particularly impressive in the patients who had stainless steel wire closure of the abdominal wall, as the sutures were closely invested with radiopaque material. From the fourth to the twelfth month after operation the radiodensity became organized into what appeared by roentgen study to represent true bone formation with anterior and posterior cortices and a medullary canal. The lateral or oblique film taken with soft tissue technique served to bring out the bony detail (Fig. 4). It should be mentioned that among the early cases in which evidence of presumptive calcium formation was shown, the finding was overlooked in several of the roentgen studies. It was only after interest in the problem mounted that the diagnosis was made with increasing accuracy.

Among the group of 30 patients, 25 have shown definite evidence of osseous formation in the soft tissues proved by roentgen study. Three patients recently operated upon show evidence of presumptive calcium formation, but no true bone as yet has appeared in the soft tissues about the abdominal scar. Two patients had bone which was removed at subsequent laparotomy and later verified by microscopic study, but preoperative roentgen studies had not been performed in either case. Twenty-one of the heterotopic bones lay completely free in the soft tissues without attachment to adjacent skeletal structures. In the remaining 9 cases, there was evidence of union between the heterotopic bone and the ensiform process. In several instances, only a fibrous tissue band served to connect the 2 structures. These findings were proved either by roentgen study, palpation, or at subsequent operation. As previously mentioned, all but 4 of the original 30 laparotomy incisons extended to or impinged upon skeletal structures.

Twelve of the 30 patients underwent either complete or partial excision of the heterotopic bone. In 5 cases the symptomatology produced by the bony spicule was of such severity as to warrant excision. In 4 patients, 2 of whom were seen during our early experience, the possibility of recurrent carcinoma in the abdominal wall was

thought to exist. At re-exploration, however, only osseous formation was encountered in the abdominal scar. One patient underwent excision of the bone growth during operation for repair of a hiatal hernia. In 2 additional patients operated upon for other reasons, a partial excision of the bone was performed. In the remaining 18 patients, there has been no indication for removal of the heterotopic growth.

Nine of the 12 patients who underwent removal of the heterotopic bone had originally undergone laparotomy through an upper abdominal midline incision or a midline incision with a lateral component (Kehr). In each instance at reoperation heterotopic bone was located in the midline fascia (Fig. 5). In 5 cases the bone was attached to the ensiform process by osseous union, and in removal of the bone the ensiform process was usually excised with the specimen. In 3 patients who had previously undergone low paramedian incisions, the bone was found to lie between the anterior rectus sheath and rectus muscle.

The excised osseous specimens varied in length from 3 to approximately 15 cm. and each was narrow in width, curved in contour, and strongly resembled a rib in gross appearance (Fig. 6). On histologic study, each of the 12 specimens showed the presence of cortical bone with active bone marrow, and 9 of the 12 demonstrated cartilaginous formation. The 12 patients have been followed for a period varying from 12 months to 9 years, and there has been no instance of recurrent or additional bone formation.

The 30 patients who compose the entire series have shown no evidence of heterotopic bone formation elsewhere. Several of the patients have since undergone laparotomy for other conditions through incisions of the longitudinal and transverse types. No patient has shown evidence of parathyroid dysfunction. Twenty-two of the 30 patients have undergone repeated determinations of serum calcium, phosphorus, and alkaline phosphatase levels. Each determination has been within the range of normal. Results of quantitative creatinine and calcium urinary studies have not been abnormal.

EXPERIMENTAL OBSERVATIONS

An attempt was made to produce heterotopic bone formation in the experimental animal.

Twenty mongrel dogs were divided into 2 groups of 10 each. In the Group I experiments, performed under Surital anesthesia and with aseptic technique, an upper midline and both right and left paramedian incisions were placed in each animal. A strip of perichondrium was then elevated from the ensiform process with care taken to maintain its inferior attachment. The strip was turned down and placed in the midline incision. Thirty milliliters of the animal's blood was injected into the right paramedian wound and a 1 by 0.5 cm. sliver of free ensiform cartilage was placed in the left paramedian incision.

Fig. 4. Eight weeks after operation definite evidence of osseous formation is noted.

Fig. 5. The osseous growth is demonstrated lying in the midline fascia. The superior aspect of the growth has an attachment to the ensiform process.

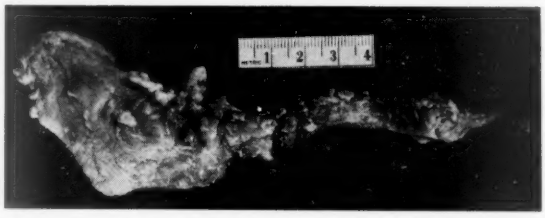


Fig. 6. Excised specimen consists of the ensiform cartilage and the heterotopic bone. The bone closely resembles a rib.

In the second group, which consisted of 10 animals, incisions were placed as in the Group I dogs. A sliver of bone and cartilage from the ensiform process was fashioned with the periosteal atachment remaining inferiorly. The sliver was turned down and positioned in the midline incision. A free strip of periosteum was placed in the right paramedian incision and bone chips obtained from a rib were put in the left paramedian incision. All wounds were closed in layers with interrupted silk sutures (Fig. 7).

The animals were sacrificed at the end of 6 months. The wounds were removed en bloc, the tissue carefully dissected, and microscopic sections made. No evidence of heterotopic bone formation was detected on gross examination of the abdominal scars among the 20 animals during the 6-month period of observation.

In the Group I animals at sacrifice, microscopic study of the tissue removed from the midline scar in which an attached strip of perichondrium from the ensiform process had originally been placed showed evidence of actively proliferating cartilage in 8 of the 10 animals. Four of the 8 had islands of cartilage in areas separated from the perichondrium (Fig. 8). The site of previous blood injection in the right paramedian scar showed no evidence of bone or cartilage formation. The left paramedian scar which originally had contained a piece of free ensiform cartilage showed evidence of resorbing cartilage in 8 instances, while in 1 animal a small area of bone formation with active marrow was noted.

In the Group II animals, microscopic study of the midline scar which had contained a sliver of attached bone and cartilage from the ensiform process showed bone resorption and fibrosis in each of the 10 animals. The cartilage was still viable, but was undergoing resorptive changes. The right paramedian scar which had contained a free strip of periosteum showed fibrosis of the periosteum in each case. Studies of the left paramedian scar which had contained free bone chips showed active viable bone in only 1 of the 10 animals.

DISCUSSION

Heterotopic osseous formation occurring in abdominal wall scars has been an intriguing phenomenon to pathologists and surgeons. Apparently the first collective review of documented cases was published in 1926 by Bouton[2] in a thesis prepared for Le Docteur en Médecine. He gives credit to Askanazy for presenting the first authenticated case before the German Society of Pathology in 1900. Rixford published an ac-

count of a case in 1903 and cited the microscopic findings. In 1905 von Eiselsberg, in reporting on 258 gastric operations, mentioned 1 instance of heterotopic osseous formation. Cases were recorded in 1907 by Kopke and Rubesch and by Lecene in 1909. Bouton was able to collect a total of 30 cases of heterotopic osseous formation. He also observed that 20 of the 30 patients had undergone gastric operations and that the bone growths were found in the upper midline area of the abdominal wall. In addition, isolated cases of heterotopic bone were also found in the inguinal area after hernia repair and in appendectomy and umbilical herniorrhaphy scars. In 1 case bone formation occurred after marsupialization of a liver cyst. The vast majority of the patients were men, with an age range extending from 13 to 70 years. Twelve of the 30 patients had wounds which had healed cleanly by first intention, whereas in 18 patients some type of wound complication had taken place. Only 1 instance of postoperative hematoma formation occurred.

Since the report of Bouton, several articles have appeared citing isolated cases of heterotopic osseous formation.[5, 6] Six cases were reported by Sanders[20] in 1955. No doubt the formation of bone growths in laparotomy scars is more common than was formerly thought. The heterotopic growth may at times be small indeed, and when asymptomatic can easily escape clinical detection. Physicians unfamiliar with the occurrence of heterotopic osseous formation may believe that only induration and excessive cicatrix exist in the abdominal wall scar when actually bone is present. In addition, no doubt, cases have been diagnosed and never recorded in the surgical literature.

Several theories have been proposed in attempts to explain the development of heterotopic osseous formation. One concept is that during muscle strain particles of periosteum are avulsed from the bony insertion of the muscle. The particles of periosteum in turn lodge in the muscle fibers and initiate osseous growth. Another theory postulates that bone formation stems from cell metaplasia as a result of muscle, tendon, or soft tissue injury. Leriche and Keith[11] believed that osteoblastic function could be assumed by cells from any part of the body besides the skeletal system. Calcium salts in turn were thought necessary for the production of bone formation, along with possible unknown enzyme mechanisms. Lyall[14] stated that heterotopic bone formation resulted from injury to a bony or cartilaginous structure, presumably through the release of osteoblasts. German observers have emphasized the frequency of pulmonary complications in patients who developed heterotopic bone formation. They believe that coughing and retching during the postoperative period produces increased strain upon the wound with resultant excessive scar tissue deposition and later bone formation.

It is of interest that in all reported cases, heterotopic bone formation has occurred in longitudinal operative scars. In no instance has it been cited in a transverse abdominal

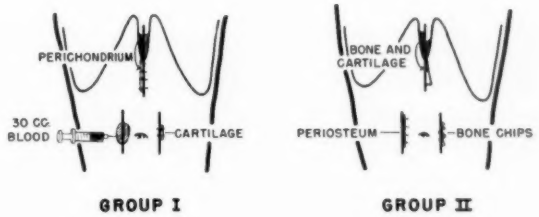


Fig. 7. Experimental incisions in 20 dogs.

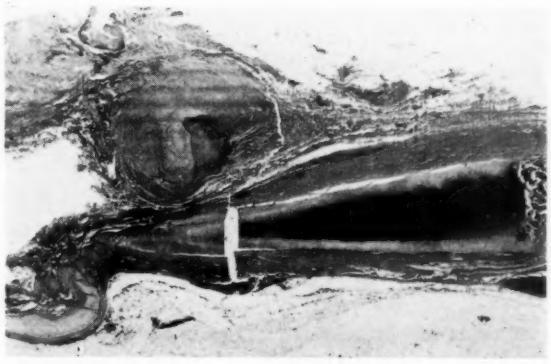


Fig. 8. Active cartilage proliferation is seen after 6 months in dogs that originally had an attached flap of perichondrium sutured in the midline wound.

wall scar. In longitudinal wounds the forces of stress are undoubtedly greater and perhaps muscle fibers under tension may be torn from their periosteal insertions and later undergo bone formation.

The presence of bone elsewhere than in the skeleton has long interested students of osteogenesis. Heterotopic bone formation has been frequently encountered in the wall of a sclerotic artery.[3] It also has been observed in pulmonary tissue, in uterine myomas, and in the dura mater.[7] It has also been reported to occur in the eye after a destructive process. Less frequently heterotopic bone has been encountered in areas of squamous-cell carcinoma of the skin,[17] in areas of breast carcinoma, and in lymph nodes. It has also been reported in the Fallopian tube[1] and in tonsillar tissue. Phemister[18] described heterotopic bone in the pedicle attachment of a renal calculus to the kidney pelvis. Bony growths have also been noted in the abdominal wall after operations on the urinary bladder.[12] Experimentally, osteogenic tissue with a well-developed marrow cavity has been produced in the kidney by ligation of its vascular pedicle.

Neuhof[16] apparently was the first to transplant fascia into the urinary bladder and to observe subsequent bone formation in the transplants. In excellently performed experimental studies, Huggins[8, 9] showed that transplants of bladder, ureter, and renal pelvis epithelium, when deposited into certain parietal fascias such as the rectus sheath or fascia lata, developed osteogenic changes. The fibroblasts surrounding the surviving transplants undergo osteoblastic transformation and true bone formation. Strangely, fibroblastic elements in certain other connective tissue areas did not respond to the epithelial stimulus. The urinary tract epithelium was found to possess an osteogenetic power which was not observed in epithelial transplants from other tissues such as stomach or small intestine. Huggins[10] later showed that proliferating gall bladder epithelium in the dog and guinea pig is capable of stimulating bone formation when transplanted into certain connective tissues such as the abdominal wall. Connective tissue areas in other parts of the body did not share in this tissue reaction and resisted the bone stimulus of the transplanted epithelium. He concluded that there was a different physiologic response among connective tissues that were morphologically similar.

Loewi[13] implanted bits of urinary bladder from guinea pigs into the chest wall, belly wall, knee joint, and lip of the same animals. Bone was formed in the granulation tissue surrounding the bladder implants. Rush and Clifton[19] used autogenous bladder mucosa for the reconstruction of tracheal rings in dogs. As a result bone grew actively in the peritracheal tissues. In most experimental studies muscle injury, injection of calcium salts, introduction of synovial fluid into the wound, hematoma production, or combinations thereof have failed to produce true bone formation. Evidence of calcification alone, however, has been produced in many instances.

The experimental findings in the present study were disappointing. In no instance was a sliver of grossly detectable heterotopic bone produced. However, when an attached strip of perichondrium from the ensiform process was placed in the midline fascia, at the end of 6 months there was microscopic evidence of actively proliferating cartilage in 8 of the 10 scars. Also, in 1 case there was microscopic evidence of bone with marrow formation where a free sliver of ensiform cartilage had been placed in the wound. It is possible that a palpable sliver of heterotopic bone might have been produced had these animals been observed for longer time periods. However, heterotopic bone formation developing in the human being has usually been detected grossly in most instances within a 6-month period after operation.

McCurrich[15] observed that with few exceptions all reported instances of heterotopic bone formation had occurred in upper midline abdominal incisions. No associated cartilage formation was present in the cases he reviewed. Nine of the 12 patients who un-

derwent bone removal in the present series showed evidence of active cartilage formation on microscopic study. This may be explained by the fact that the bone growths in our series were excised relatively early. It should be re-emphasized that in 26 of our 30 cases the original laparotomy incision extended to or impinged on skeletal structures, either bone or cartilage. In 21 of the 30 cases it was the clinical and radiographic impression that the bone growth lay free in the soft tissues of the abdominal wall, with no demonstrable attachment to skeletal structures. In the remaining 9 cases there was either fibrous or bony attachment between the heterotopic bone and the ensiform process. Of the 12 patients who underwent removal of the heterotopic bone, 5 were found to have an osseous attachment between the heterotopic bone and the ensiform process. In 9 of the 12 patients the bone was located in the midline fascia. In the remaining 3 patients, who had previously undergone low paramedial incisions, the bone was found to lie between the anterior rectus sheath and rectus muscle.

With the preponderance of the reported cases of heterotopic osseous formation having occurred in upper midline abdominal incisions and usually after operation on the stomach, one cannot help but believe that injury to the ensiform process might play an important role as an etiologic agent. Most of our cases followed operations for duodenal ulcer and the original incision had been purposely extended to the ensiform cartilage, or above and to the left of that structure, to gain added exposure in the performance of vagotomy. On occasion, the authors distinctly remember having actually incised the substance of the ensiform process in entering the abdomen.

It is our present belief that considerable care should be exercised to avoid this technical error. Should the ensiform process be inadvertently injured by incision, partial excision, or trauma from retractors, serious consideration should be given to its removal. Also, it is no doubt important that in closing the upper midline incision care should be taken not to pass the needle point into the periosteum overlying the ensiform process. Should this occur, it is quite possible that the trauma produced could excite osseous proliferation.

The heterotopic bone will necessitate removal only in instances in which symptoms arise from its presence. In all other cases the exact nature of the presenting mass should be explained to the patient and this, along with reassurance, is all that is necessary. Should indication for removal of the bone arise, then complete excision, including removal of the ensiform process, is the method we advise.

The occurrence of heterotopic bone in low midline or low paramedial incisions has rarely been encountered. It has developed in circumstances in which the incision was several centimeters removed from the pubic osseous structures. The development remains even a more perplexing mystery than does the osseous growth which develops in upper abdominal scars.

SUMMARY

Thirty cases of heterotopic bone formation which occurred in laparotomy scars have been reviewed. The clinical and roentgen findings associated with heterotopic osseous growths have been described. Indication for excision of such growths is stated.

Attempts to produce heterotopic osseous formation in wounds of the experimental animal have been described.

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Evaluation of portal circulation by percutaneous splenic isotope injection

SEYMOUR I. SCHWARTZ, M.D.*
ROBERT H. GREENLAW, M.D.**
ROCHESTER, N. Y.
From Departments of Surgery and Radiology, University of Rochester School of Medicine and Dentistry

Evaluation of the portal circulation has provided the basis for establishing a diagnosis of esophageal varices and determining the patency of a portacaval shunt. This evaluation has been greatly refined by measurements of splenic pulp and hepatic vein wedge pressures and by the more liberal use of percutaneous splenoportography. More recently, techniques of isotopic evaluation have been applied to the portal circulation.

Deterling and associates[3] instilled radioactive sodium into the rectum and, by means of counting over the brachial artery, were able to determine the patency of portacaval shunts. Sigel and coauthors,[16] using Na^{22} injected submucosally into the colon, demonstrated an absence of clearance associated with obstruction of the portal vein. Long and his colleagues[7] injected Kr^{85} into the spleen of dogs and noted that the appearance and peak times of radioactivity measured in the expired air were significantly reduced in the presence of a patent portacaval shunt.

Mena and his group[10, 11] used twin scintillation detectors placed over the heart and liver to record the appearance of radioiodinated serum albumin (RISA), injected intravenously, in an effort to determine cardioportal circulation times. Finally, Iber and associates[5] investigated intrasplenic injection of an isotope with continuous sampling of hepatic and peripheral venous blood as a method of determining portal collateral flow in patients.

Our study with simultaneous external monitoring of the areas over the liver, right heart, and esophagus after percutaneous injection of an isotope into the spleen, has established diagnostic patterns for the normal and for a variety of abnormal types of portal circulation.

MATERIALS AND METHODS

A Picker dual detection system (Fig. 1) was utilized in all laboratory and clinical studies. The system provided twin scintillation probes, twin rate meters and twin chart recorders. This permitted simultaneous recording of radioactivity in 2 areas of the body. One detector was placed over the right lobe of the liver and directed slightly laterally. The second probe was positioned over the right heart-lung root and included in its field of response the lower half of the esophagus. The rate meters were operated at 0.5 second time constants and the recorders were set at a speed of 12 inches per minute. The recorders were capable of full-scale response in 250 msec. and thus did not add delay to the meter response. Several tracer materials, including Radiorenographin and Hipputope,* were used. The only specification considered was a short biologic half-life. The laboratory and clinical studies were performed with 30 to 100 μc of radioiodine in a volume of 1.0 ml. or less.

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*John and Mary R. Markle Scholar.

**Advanced Clinical Fellow in Radiation Therapy under the American Cancer Society.

*E. R. Squibb & Sons.

Fig. 1. Dual detection system with twin scintillation detectors, twin rate meters, and twin chart recorders.

Laboratory studies. Adult mongrel dogs were anesthetized with pentobarbital sodium and a laparotomy was performed. In the control series, after the probes had been positioned over the right lobe of the liver and the right heart-lung root, the isotope was injected into the parenchyma of the spleen under direct vision and simultaneous recordings were made. In other experiments, either the portal vein or splenic vein was occluded prior to splenic injection and, after the initial pattern had been recorded, the occlusion was released and a second pattern demonstrated. The final preparations studied were animals with patent and thrombosed end-to-side portacaval shunts.

Clinical studies. All studies were carried out with the patient in the supine position. Percutaneous splenic puncture was performed through the ninth intercostal space in the posterior axillary line after this region had been anesthetized with 3 to 5 ml. of 1 per cent Xylocaine. Measurements of splenic pulp pressure were made in all patients and, in the majority of the patients, concomitant splenoportography was carried out to correlate the findings of this accepted procedure with the results of the isotope curves. The radiologic technique included 3 exposures taken in rapid sequence beginning at the end of injection. In the latter group a No. 18 or 19 needle was used. Patients who were hemorrhaging massively or who for other reasons were studied in the Emergency Department or on the wards, did not undergo roentgenographic studies. In these cases a No. 20 needle was used to measure pressure and inject the isotope.

RESULTS

Laboratory studies. Injection of 30 μc of I^{131} into the spleens of 3 dogs and into the splenic vein of 1 dog produced similar results (Fig. 2). Radioactivity appeared in the liver in less than 2 seconds. The appearance slopes were steep and the plateau began to decrease after approximately 12 seconds. The isotope gradually appeared in the right heart-lung root 15 to 17 seconds after injection, concomitant with the decrease from the peak of radioactivity in the liver.

In 3 dogs with temporary occlusion of the portal vein, no radioactivity was monitored by either detector after splenic injection of 30 μc of I^{131}. This situation persisted throughout the period of occlusion and, when the occlusion was released in 2 of the dogs, tracings similar to those of the controls resulted. The animal with sustained occlusion continued to show no radioactivity in the liver or right heart-lung root.

Injection of isotope into the spleens of dogs with patent end-to-side portacaval shunts demonstrated a rapid appearance (less than 2 seconds) and a high peak in the right heart-lung root. A minimal temporary rise ("blip") over the liver was noted which reflected the passage of I^{131} through the inferior vena cava as it coursed behind the liver. No radioactivity was monitored over the liver or heart after splenic injection of I^{131} in a dog with an end-to-side portacaval shunt which had been thrombosed several hours prior to study. Direct injection of the isotope into the vena cava caudad to the liver yielded tracings similar

to those obtained with splenic injections in dogs with patent portacaval shunts. A high peak of radioactivity appeared over the right heart-lung root in less than 2 seconds and a transient "blip" in the region of the liver which reflected retrohepatic caval flow was also noted.

Clinical studies. The patients studied were classified into 5 major groups and a consistently distinctive pattern was demonstrated for each group. The 5 groups included normal patients and patients with portal hypertension without varices, with esophageal varices, with portal vein thrombosis, and with portal-systemic shunts. The individual times for appearance, peak, and plateau of the radioactivity over the liver and the right heart-lung root (esophagus) are listed in Table I. "Appearance time" refers to the number of seconds from initiation of splenic injection until the scintillation detector responded to radioactivity. "Peak time" indicates the duration between isotope injection and maximal radioactivity. In instances in which maximal activity over the liver was temporarily sustained, the interval between the onset of maximal activity and the beginning of decrease from this peak was computed and is defined as "plateau time." This measurement was used to evaluate the rate of flow through the liver.

Twenty-five isotopic evaluations of the portal circulation were performed on 20 patients. Fifteen of these patients were studied in the Radiology Suite to permit correlation of the splenoportography and the remaining investigations were performed at the patient's bedside.

Normal patients. The normal patterns of the simultaneous isotope tracings are shown in Fig. 3. As noted in these tracings, the appearance in the liver and the peak occurred early. The hepatic plateau was not prolonged. The detection of radioactivity over the right heart-lung root was delayed, followed the liver peak, and was concomitant with the decrease in liver radioactivity. This isotope evaluation anticipated the patient's normal splenoportogram.

Normal tracings were demonstrated in 5 patients who were studied to determine either the cause of upper gastrointestinal bleeding or splenomegaly. In each instance, the appearance and peak of radioactivity in the liver significantly preceded the appearance and peak times over the right heart root. In all patients the splenic pulp pressures were normal, that is, less than 160 mm. H_2O. The 3 patients in whom splenoportography was carried out demonstrated normal hepatic arborization with no evidence of collaterals.

Patients with portal hypertension without varices. In this group, the typical tracings demonstrated a delay in the spleen-to-heart circulation coupled with normal spleen-to-liver times. The appearance and peak time for radioactivity over the liver were rapid and similar to those in the normal study. The pertinent diagnostic finding in this group of patients was a prolongation in circulation through the liver as noted in the plateau times (Table I). Four patients with

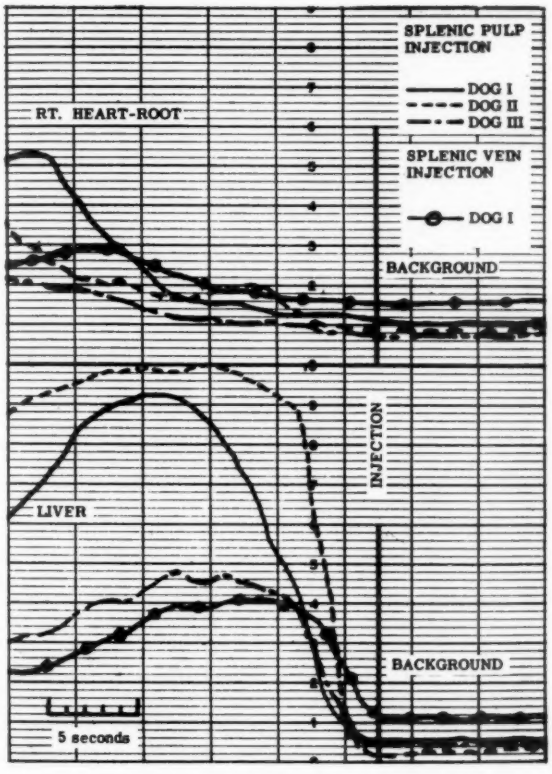

Fig. 2. Injection of isotope (30 μc of I^{131} as sodium iodide, 0.5 second time constant, 30 K maximum response, 12 inches per minute) into splenic pulp and vein of normal dogs.

Table I. *Isotopic evaluation of portal circulation*

Patient	Liver			Right heart root (esophagus)	
	Appearance (sec.)	Peak (sec.)	Plateau (sec.)	Appearance (sec.)	Peak (sec.)
Normal patients					
E. S.	0.5	3	2	6	21
F. R.	1	5	7	10	22
G. R.	1	4	6	10	17
A. L.	1	3	7	10	12
A. C.	0.5	6	6	10	22
Patients with portal hypertension without varices					
A. W.	0.5	3	14	10	17
J. E.	0.5	4	30	7	—
C. M.	0.5	7	10	8	18
P. B.	1	5	8	12	21
Patients with esophageal varices					
W. P.	2	7	13	0.5	7
C. G.	3	—	—	1	—
A. K.	7	12	8	3	10
S. K.	15 (trace)	—	—	5	11
R. M.	2 (trace)	—	—	0.5	8
B. M.	2	6	—	0.5	2
C. A.*	1	5	—	0.5	7
Patients with portal vein thrombosis					
E. K.	No radioactivity			12 second (trace)	
Patients with portal-systemic shunt					
E. G.	Transient rise (inferior vena cava)			4	7
R. M.	Transient rise (inferior vena cava)			4	8
C. W.	Transient rise (paraumbilical vein)			7	10

*Gastric varices seen on portogram. No coronary vein or esophageal varices visualized. Esophagoscopy demonstrated small varices.

cirrhosis confirmed by liver function studies and, in some instances, by needle biopsy were classified in this group. All of these patients had portal hypertension as evidenced by splenic pulp pressures in excess of 220 mm. H_2O. In each of these patients no collaterals could be demonstrated on splenoportography.

Patients with esophageal varices. Seven patients with esophageal varices secondary to portal hypertension were studied. It is to be stressed that, in the situation of esophageal varices, the probe over the right heart root was essentially monitoring response in the lower half of the esophagus. In each case (Table I), the diagnostic finding of a spleen-to-liver appearance time greater than the spleen-to-esophagus appearance time was apparent. The right heart root (esophageal) peak was also earlier and higher than that detected over the liver area, which indicated preferential flow via the coronary vein and ancillary collateral veins. Representative simultaneous isotope tracings are shown in Fig. 4.

All 7 patients had the diagnosis of esophageal varices substantiated by splenoportography, barium swallow, or esophagoscopy. Patient C. A. was unusual in that although the istotope appeared first over the esophagus, the peak was earlier and higher over the liver. Small gastric varices were seen on the portogram but the coronary vein, esophageal varices, and major collaterals were not visualized. Esophagoscopy showed small varices in the distal end of the esophagus.

One patient was studied at the bedside after a Sengstaken-Blakemore tube had been inserted as treatment for bleeding esophageal varices. The initial tracings were recorded with the esophageal balloon inflated to a pressure of 45 mm. Hg. Fig. 5, *A* shows the tracing with the balloon inflated and demonstrates a gradual slope of radioactivity in the right heart root (esophagus) as con-

trasted with the steep slope seen when the balloon was deflated (Fig. 5, *B*).

Patients with portal vein thrombosis. One patient, E. K., with acute thrombosis of the portal vein, was investigated. This patient had rapid onset of ascites and distended abdominal wall veins 10 days after drainage of an empyema of the gall bladder. Studies performed 3 weeks after the suspected portal vein thrombosis showed no appearance of I^{131} over the liver and a very gradual and minimal evidence of radioactivity in the right heart root (Fig. 6). A splenoportogram recorded the pathologic anatomy.

Patients with portal-systemic shunt. Three patients with portal-systemic shunts were included in this category (Table I). In each case, although the I^{131} appeared relatively early in the right heart root, the impressive finding was the occurrence of an early and extremely high peak of radioactivity in this region. It is to be noted that with a portal-systemic shunt the appearance did not occur as rapidly as in the group of patients with esophageal varices. However, the peak was significantly earlier and higher. This difference in appearance time was to be anticipated since, in the case of a portal-systemic shunt, the course of the isotope was from spleen to splenic vein to inferior vena cava and finally to right atrium where it was detected. In comparison, the flow of isotope in patients with esophageal varices was from spleen to splenic vein to coronary vein and esophagus where it was monitored earlier.

Two of the patients were studied subsequent to a surgically created end-to-side portacaval shunt. A set of representative tracings is shown in Fig. 7. In this situation, the transient rise over the region of the liver reflected the flow of isotope through the inferior vena cava as it passed behind the liver. C. W., the third patient in this group, was investigated because of marked meat intoxication associated with minimal abnormalities in the liver function tests. The transient rise in the region of the liver and the rapid and high peak over the right heart root suggested a large pathologic portal-systemic shunt. The splenoportogram con-

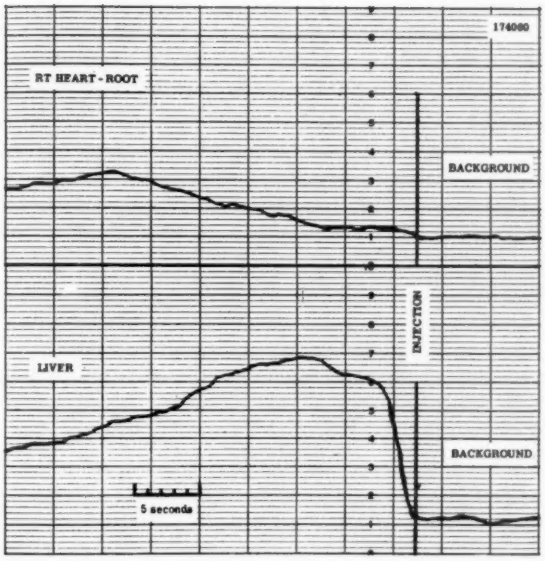

Fig. 3. Normal simultaneous tracings (100 μc of I^{131} as Renographin, 0.5 second time constant, 100 K maximum response, 12 inches per minute).

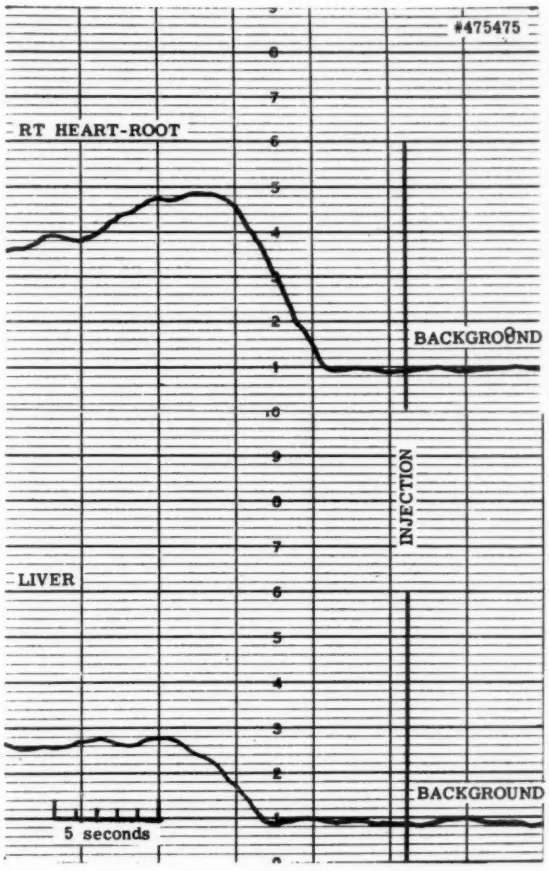

Fig. 4. Simultaneous tracings from patient with esophageal varices (100 μc of I^{131} as ISA, 0.5 second time constant, 100 K maximum response, 12 inches per minute).

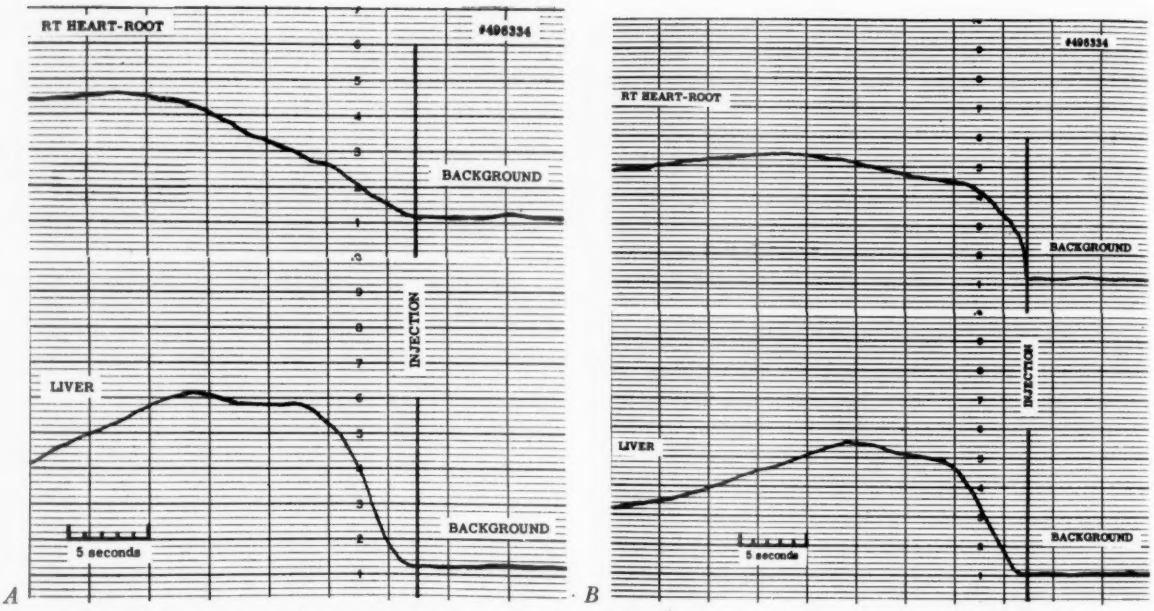

Fig. 5. *A*, Esophageal varices (50 μc of I^{131} as Renographin, 0.5 second time constant, 30 K maximum response, 12 inches per minute). Esophageal balloon inflated. *B*, Esophageal balloon deflated.

firmed this pathologic process and demonstrated a large paraumbilical vein and an absence of flow through the liver.

DISCUSSION

The isotopic evaluation of portal circulation is particularly applicable to the differential diagnosis of acute upper gastrointestinal bleeding. Esophagogastric varices have been implicated as the cause of massive hematemesis in 32 per cent[18] of the patients. Since the management of bleeding varices differs significantly from that of the other causes, it is important to establish a diagnosis on an emergency basis.

Efforts directed at early diagnosis have been suggested. Esophagoscopy requires a skilled endoscopist and interpretation is difficult during the active phase of bleeding. As an elective study, barium swallow has a high percentage of false-negative results which is increased during the acute bleeding episode.[6]

Tests of liver function, such as the Bromsulphalein test, have proved unreliable since they define the presence of liver disease but not necessarily varices.[9] The qualitative test for hyperammoniemia as described by McDermott[9] is more pertinent because the elevation of the ammonia level is due to an extensive portal-systemic collateral circulation and is not indicative of hepatic function. However, as pointed out by the author, pretreatment with antibiotics, glutamic acid, or arginine will negate the value of this test. Also, any large portal-systemic collateral such as a paraumbilical vein or a portarenal shunt will cause a positive result in the absence of esophagogastric varices. Finally, McDermott presented a documented case of hemorrhage from varices with a negative qualitative test result and a quantitative ammonia determination which showed only slight elevation.

Esophageal balloon tamponade has been used but presents certain disadvantages. Reports have indicated failure to control hemorrhage in 25 to 55 per cent of patients with bleeding varices.[4, 8, 12, 14, 15] Also, bleeding from gastric ulcer has been completely arrested by this apparatus.[1] In addition, the hazards associated with tamponade are significant.[2]

Panke and associates[13] proposed splenic pulp manometry as an emergency test. A 90 per cent accuracy was reported, but there was a zone of splenic pulp pressures which included those of patients bleeding from varices and from other causes. In our limited

series, we have noted 4 patients (Table I) with portal hypertension unaccompanied by the development of pathways of collateral flow. Furthermore, the admittedly rare situation of esophageal varices associated with normal portal pressures would not be diagnosed by this technique.

Splenoportography affords diagnostic evidence of esophageal varices in a very high percentage of cases but requires an experienced team of technicians. It is rarely used for patients who are actively bleeding since transportation to the Radiology Department and patient cooperation are difficult to achieve.

The technique of isotopic evaluation of portal circulation proposed in this study is simple, can be performed at the patient's bedside, and, therefore, is applicable to patients with massive hematemesis. The dual detector system is run by 1 man and minimal training is required. Diagnosis can be made immediately and interpretation is not dependent upon techniques of exposure and development as in the case of splenoportography. In addition, for the emergency situation when the prothrombin time is not always available, the dangers of splenic rupture and hemorrhage are theoretically reduced since only a small-bore needle and a 1 ml. bolus are introduced into the spleen. Finally, in the patient with acute bleeding to whom balloon tamponade is applied as emergency treatment, the efficacy of the pressure may be determined by comparison of the initial tracing with a second series taken with the balloon inflated.

For elective preoperative studies, isotopic investigation of portal circulation complements splenoportography. While the latter demonstrates the pathologic anatomy, the former permits an evaluation of the dynamic physiologic function of the portal circulation. After insertion of the needle, the injection of the isotope and the monitoring of radioactivity over the liver and heart are used to indicate correct intrasplenic position of the needle. Measurement of the splenic pulp pressure and the splenoportogram are then performed in rapid succession without removal of the needle. Also, by determining the appearance and peak times of radioactivity over the liver, heart, and esophagus, the roentgenograms can be timed for optimum demonstration of the anatomy. Postoperatively, the technique graphically demonstrates the patency or occlusion of a portacaval shunt.

A qualitative determination of the dynamics of flow, rather than a static picture, is particularly appropriate in the investigation of hepatic-portal encephalopathy. This neuropsychiatric syndrome of liver disease is more closely related to the extent of collateral blood flow than to the degree of portal hypertension or to the presence of a specific collateral vessel.[17] The technique of simultaneous isotope detection proposed in this study provides a direct evaluation of relative flows through the liver and along the course of bypassing portal-systemic shunts.

SUMMARY

After percutaneous injection of isotope tracer compounds into the spleen, circula-

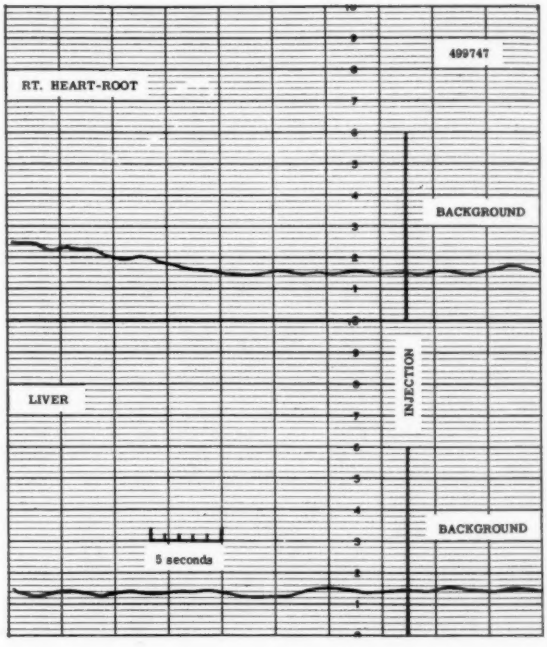

Fig. 6. Simultaneous tracings from patients with portal vein thrombosis (40 μc of I^{131} as Hiputope, 30 K maximum response, 0.5 second time constant, 12 inches per minute).

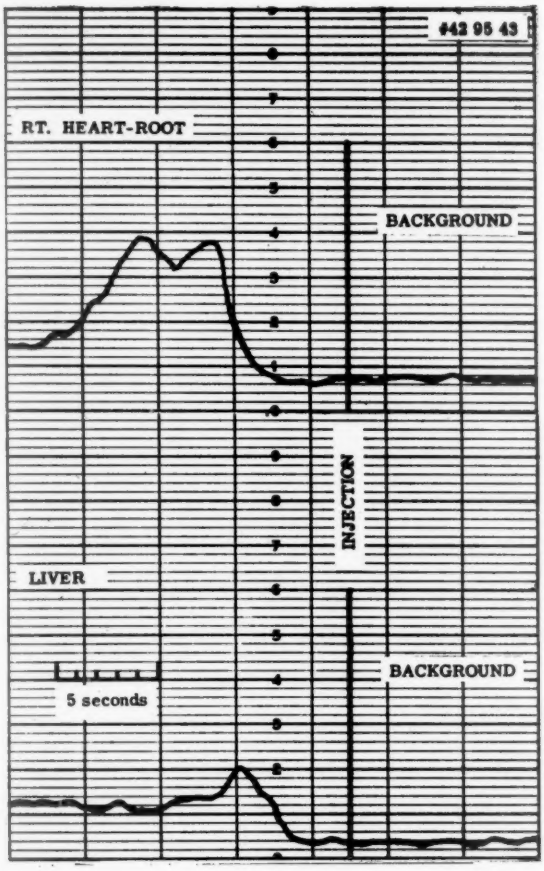

Fig. 7. Simultaneous tracings from patients with patent end-to-side portacaval shunts (30 μc of I^{131} as sodium iodide, 0.5 second time constant, 30 K maximum response, 12 inches per minute).

tion times to the liver, right heart, and esophagus are measured simultaneously by means of twin scintillation detectors. The relative appearance times, peaks, and durations of sustained radioactivity over the liver and right heart (esophagus) afford a clear appraisal of portal circulation.

Diagnostic patterns of isotope flow are established for 5 clinical situations—normal, portal hypertension without varices, esophageal varices, portal vein thrombosis, and portal-systemic shunts.

The advantages of the technique are simplicity and adaptability for use at the patient's bedside. Its use in the emergency differential diagnosis of upper gastrointestinal bleeding is emphasized. For elective evaluation, the isotope study complements the splenoportogram and is particularly applicable to the investigation of hepatic-portal encephalopathy.

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Complete homograft replacement of the heart and both lungs

RICHARD R. LOWER, M.D.*
RAYMOND C. STOFER, D.V.M.
EDWARD J. HURLEY, M.D.*
NORMAN E. SHUMWAY, M.D.**
PALO ALTO, CALIF.
From the Department of Surgery, Stanford University School of Medicine

The failure of previous attempts at experimental homotransplantation of the heart and both lungs has been attributed to respiratory paralysis.[7, 17] The observations to be reported demonstrate that complete homograft replacement of the heart and lungs is at present technically feasible and that spontaneous respiration resumes which will sustain life until homograft rejection supervenes.

METHOD

Mongrel dogs which weighed 14 to 17 kilograms were used in these experiments. The donor and recipient animals were anesthetized intravenously with 30 mg. of pentobarbital sodium per kilogram of body weight, intubated, and ventilated with 100 per cent oxygen. The donor was prepared by exposure of the thoracic organs through the right fifth intercostal space. The azygos vein was ligated and divided. The superior and inferior venae cavae were mobilized for division at least 2 cm. from the right atrium. The heart and lungs were further mobilized by division of the pulmonary ligaments, the diaphragmatic reflection of the pericardium, and the anterior mediastinal reflection of the pleura. Tapes were passed about the venae cavae, ascending aorta, and trachea. Two milligrams of heparin per kilogram was injected intravenously.

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*Fellow, National Heart Institute, United States Public Health Service.
**Established Investigator, American Heart Association.

A similar thoracotomy incision was made in the recipient animal. The heart and lungs were mobilized and careful hemostasis utilized. The phrenic nerves were dissected free of the pericardium and preserved. Ligation of the bronchial vessels with careful preservation of the vagus nerves required meticulous dissection of the posterior mediastinum. Heparin in a dosage of 2 mg. per kilogram was administered and the animal was prepared for cardiopulmonary bypass. The venous cannulas were inserted peripherally through the right jugular and femoral veins and the catheter tips were advanced to a position approximately 3 cm. from the right atrium. Oxygenated blood was returned to the animal through a cannula in the femoral artery. After institution of cardiac bypass, the venae cavae were occluded with noncrushing clamps just proximal to the venous catheter tips, the ascending aorta was clamped near the bracheocephalic vessels, and the heart and lungs were removed by division of the venae cavae, trachea, and aorta just distal to the coronary ostia. During bypass the animal's temperature was lowered to 28° to 30° C. by priming of the oxygenator initially with cold blood.

Excision of the donor heart and lungs was accomplished rapidly; the vagus and phrenic nerves were not preserved and the bronchial vessels were not ligated. A 1 cm. cuff was left on the venae cavae and on the ascending aorta, and the trachea was divided about 2 cm. above the carina. The donor organs were immediately immersed in normal

saline solution at approximately 4° C. for 10 minutes and no saline was allowed to enter the trachea. After being cooled in this manner, the heart and lungs were placed in the recipient thorax and anastomosis of the aorta, trachea, and venae cavae carried out with fine silk sutures. The caval and aortic clamps were removed to restore coronary blood flow and, after rewarming, the animal was electrically defibrillated. After 15 to 20 minutes of support by the pump-oxygenator, bypass was discontinued and the wound closed in layers. A chest catheter was left in place for postoperative drainage and penicillin-streptomycin mixture was administered daily.

RESULTS

Six recipient dogs resumed spontaneous respirations after the operative procedure. Oxygenation remained adequate but the respiratory pattern was altered in that tidal volume was increased and the respiratory rate was diminished. There was an occasional marked prolongation of the expiratory phase. Four of the animals died of surgical complications 5 to 24 hours after the onset of spontaneous breathing.

The remaining 2 animals recovered fully except for temporary gastrointestinal ileus, presumably due to vagus nerve injury during dissection and ligation of the bronchial vessels. They were ambulatory, active, and eating until they became lethargic on the fourth postoperative day. At this time the arterial oxygen content of 1 animal was 14.21 vol. per cent with an oxygen capacity of 18.19 vol. per cent (78.2 per cent saturation). The arterial carbon dioxide content was 48.8 vol. per cent (method of Van Slyke and Neill). Both animals died on the fifth postoperative day of respiratory insufficiency.

At autopsy the lungs of these 2 dogs were found to be heavy and firm (Fig. 1) and the tracheobronchial tree contained a considerable amount of blood-tinged exudate. The tracheal suture lines appeared to be healing in normal fashion. Microscopically there was considerable atelectasis, but the most striking finding was an extensive infiltration of large mononuclear cells which appeared to be primarily histiocytes (Fig. 2). In some areas there were perivascular infiltrates of typical plasma cells and scattered large unidentified cells resembling Dorothy Reed histiocytes. Except in a few microscopic areas, vascular thrombosis and necrosis of pulmonary tissue were absent. Grossly the heart appeared normal (Fig. 3), but microscopically showed in-

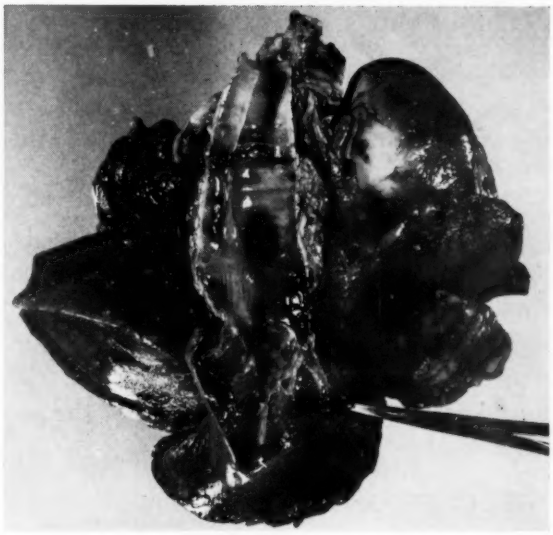

Fig. 1. The homograft heart and lungs 5 days after transplantation. The lungs are firm, heavy, and airless.

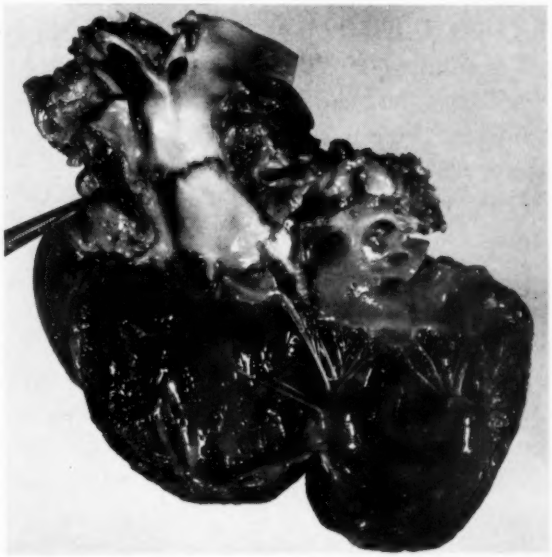

Fig. 2. The heart (same specimen as in Fig. 1) appears grossly normal 5 days after homotransplantation.

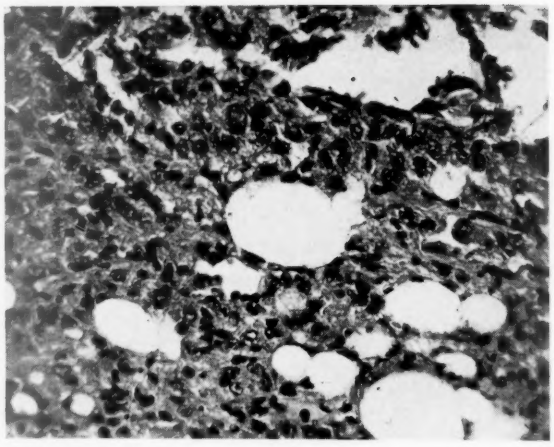

Fig. 3. Photomicrograph of the lung parenchyma shows an infiltration of histiocytes. (×525; reduced ⅔.)

filtration of the myocardium with mononuclear cells, primarily the plasma-cell variety, and a few small areas of myocardial necrosis. The changes in the myocardium were much less extensive than those observed with cardiac homografts of longer duration.[13]

DISCUSSION

Homotransplantation of the heart and lungs as a unit would have obvious clinical application in conditions in which irreparable or irreversible pathologic processes exist in both organs. This experimental study was designed, therefore, to determine the technical feasibility of such a procedure and to elucidate the effects of sacrificing the bronchial arterial supply and the pulmonary nerve supply.

The bronchial arteries were originally thought to be indispensable for nutrition of the mainstem and lobar bronchi.[3] However, experimental reimplantation of the autologous lung with subsequent prolonged observation of viability proved that the bronchial supply can be sacrificed without resulting necrosis.[10, 14, 15] The major problem which the bronchial vessels presented in this study was ligation in the recipient animal without injury to the vagus nerves which are in proximity.

The question of the possibility of prolonged survival after pulmonary denervation remains unanswered. The normal respiratory pattern occurs as a result of both central and peripheral neural control.[4] It is evident that the sacrifice of peripheral innervation which necessarily accompanies pulmonary transplantation results not in respiratory paralysis, but in an altered respiratory pattern which resembles that observed after bilateral cervical vagotomy. The adequacy of this pattern for normal ventilation over prolonged periods and for maintenance of respiratory equilibrium under various stresses remains to be demonstrated. Reimplantation of both autologous lungs or prolongation of homograft acceptance would provide the opportunity for such observations.

The histologic findings in the 2 animals which survived for 5 days are at variance with those described previously in lung homografts. Hume[9] has recently reviewed the prior experience with pulmonary homotransplantation reported by Staudacher,[16] Lanari,[11, 12] and others.[1, 2, 5, 6, 8] The early changes described by these authors were alveolar edema and polymorphonuclear leukocyte infiltration progressing to lymphocytic infiltration, vascular thrombosis, and frank necrosis of parenchymal tissue in the animals which survived for longer periods. None of these conditions was prominent in the pathologic material studied in this experiment. The prominent feature was an extensive infiltration of large mononuclear cells which apparently caused death by interference with respiration at the alveolar level.

SUMMARY

Complete homograft replacement of the heart and both lungs in the dog has been carried out with survival of 2 animals for 5 days. These animals resumed spontaneous breathing with an altered respiratory pattern. Death from respiratory insufficiency was apparently due to infiltration of mononuclear cells into the lung parenchyma.

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Use of the Cheatle-Henry approach in the treatment of cryptorchidism

SIDNEY LIPTON, M.D.
BROOKLYN, N. Y.
From Maimonides Hospital and State University of New York College of Medicine

The objective of the surgical treatment of cryptorchidism is to advance the undescended testis into the scrotum. Adequate spermatic cord length must be obtained to permit the testis to reside, without tension, in its new domicile.

The most widely used operations are the Torek[6] and Bevan[1] procedures, with various modifications. Currently, the two-stage Torek technique is in disfavor because fixation of the testis to the thigh can result in vascular impairment of the testis from tension on the cord. The Bevan procedure, which involves tedious dissection of the cord within the inguinal canal, can also lead to damage to the spermatic vessels.

In the operation popularized by Gross,[3] the cord is elongated by retroperitoneal dissection. This method is also advocated by Swenson.[5] To approach the components of the cord in their retroperitoneal position, the deep epigastric vessels are severed and the floor of the inguinal canal is divided. The vas deferens and internal spermatic vessels are then lengthened by stripping adhesive bands and peritoneum by blunt and sharp dissection. The cord is brought through the floor of the inguinal canal just above the pubic tubercle. The floor of the canal is reconstructed by suturing the transversalis fascia over the cord.

Gross' operation has several inherent defects. First, the exposure of the retroperitoneal portion of the cord is not satisfactory and a considerable portion of the dissection is done blindly. Second, the previously ligated sac is frequently torn in the dissection and closure of the thin peritoneum is difficult and frustrating. Third, the division of the inguinal floor and the creation of a new internal ring at a vulnerable site in the floor may contribute to the later development of a direct hernia. Gross[3] acknowledges this possibility, but he stated that he had not seen a direct hernia occurring postoperatively. There has been, however, no report of long-term follow-up studies.

The procedure proposed in this communication is adapted from the Cheatle-Henry[2, 4] approach and is designed to overcome the

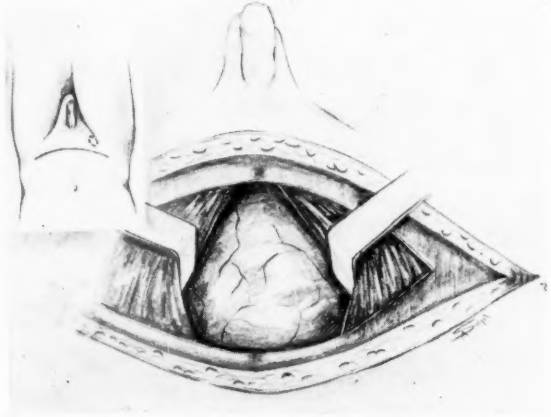

Fig. 1. The inset shows the Pfannenstiel incision. The rectus fascia has been divided transversely and dissected off the muscles. The recti are retracted to exposing the preperitoneal space.

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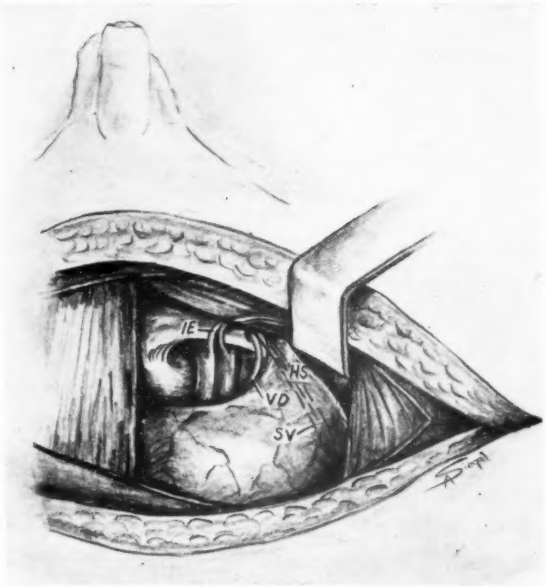

Fig. 2. The ipsilateral rectus muscle has been retracted laterally to expose the undersurface of the inguinal floor. The sac (*HS*), vas deferens (*VD*), and spermatic vessels (*SV*) are seen entering the internal inguinal ring. *IE*, internal epigastric vessels.

stated objections. I have been interested in this novel approach to groin hernias and have used the method in 20 cases. In the course of study of this technique, I was impressed with the admirable exposure of the cord structures. This led to the conclusion that the Cheatle-Henry procedure could be applied to the correction of cryptorchidism. The operation has been employed in a case of unilateral cryptorchidism and a case of bilateral cryptorchidism with complete success. A curvilinear suprapubic incision is made extending across both recti (Fig. 1, inset). The rectus fascia is divided transversely from one linea semilunaris to the other. The lower fascial flap is freed down to the pubis. The upper flap is freed for 1 inch from the underlying muscles. The recti are then separated in the midline starting at the pubis and proceeding in a cephalad direction (Fig. 1). The peritoneum is swept away from the overlying rectus and transversalis muscles. The inguinal floor, internal rings, and hernial sac are exposed (Fig. 2). The deep epigastric vessels are divided between ligatures to facilitate dissection about the internal ring. The sac stands out as a taut, funnel-shaped structure. The vessels are on the posterolateral aspect of the sac. The vas enters the internal ring independently. It can be freed and traced down to the base of the bladder. The sac is opened on its anterior aspect. The posterior wall of the sac is incised from within outward. The entire sac, now freed (at one point) from the cord, is stripped upward and a high ligation is performed. The spermatic vessels can now be dissected to the renal pedicle under complete visual control. The peritoneum is intimately adherent to the spermatic vessels. In stripping the peritoneum off the vessels, one can observe the vessels to lengthen and assume a lax position (Fig. 3). If the peritoneum is torn, it can be easily repaired. When, in the judgment of the operator, the vessels and vas have assumed sufficient length, the peritoneum is allowed to fall back. The peritoneum of the opposite side is then stripped off the anterior abdominal wall and the inguinal floor inspected for a hernia. If found, it may be corrected by excision of the sac and repair of the defect.

The skin of the inguinal portion of the incision on the involved side is retracted down-

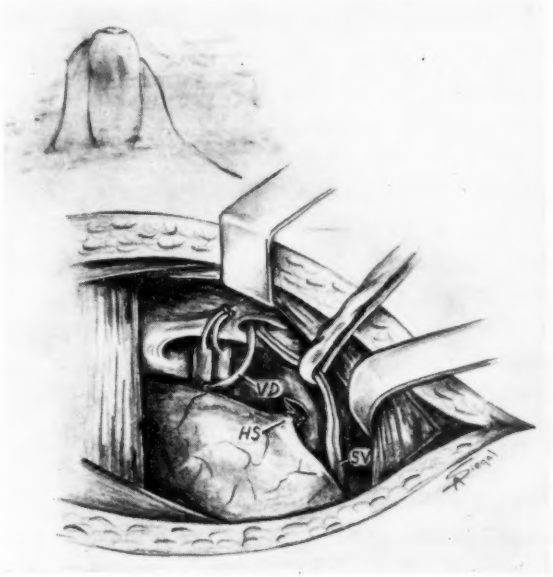

Fig. 3. The sac (*HS*) has been divided and ligated flush with the peritoneum. The spermatic vessels (*SV*) and vas deferens (*VD*) have been freed and lengthened. The inferior epigastric vessels have been divided to help expose the internal ring.

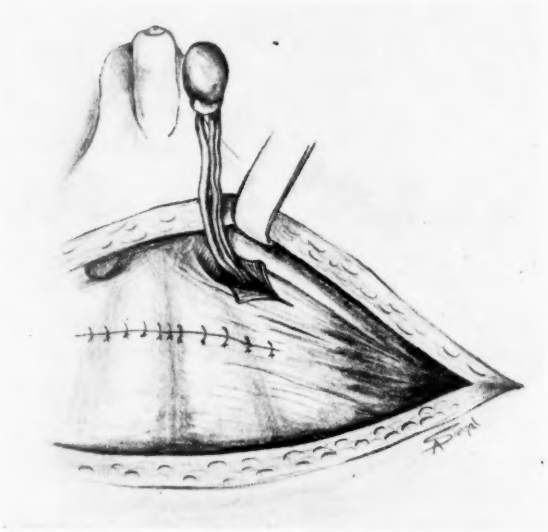

Fig. 4. The rectus muscles and fascia have been united. The inferior skin flap is retracted to expose the external ring. The external oblique fascia has been opened and the testicle and cord have been brought out in preparation for insertion into the scrotum.

ward (Fig. 4). The external ring is located and the external oblique fascia divided. The testis and cord are freed from adhesions. The distal remnant of the sac is excised. Gentle traction will bring the freed spermatic vessels and vas into the inguinal canal. If the internal ring is dilated, it is repaired with interrupted No. 3-0 silk sutures. The rectus muscles are then united in the midline with several interrupted No. 3-0 chromic catgut sutures. The rectus fascia is united with interrupted No. 3-0 silk sutures. The scrotum is then prepared for the testis. A silk suture secured to the tunica albuginea is passed through the scrotum and fixed with a rubber band to the thigh. The external oblique fascia is sutured over the cord. The superficial fascia and skin are closed.

DISCUSSION

This operation permits an unusually extensive exposure of the retroperitoneal portion of the vas deferens and internal spermatic vessels. These structures can be freed under direct vision by sharp dissection. The hernia sac can be ligated at its highest level. The integrity of the inguinal floor is preserved. There is no need for rerouting the spermatic cord. The normal internal inguinal ring and its protective sphincteric mechanism are preserved. Without an additional incision and with minimal trauma, the contralateral side can be inspected for hernia. The contralateral undescended testis may be corrected at the same operation.

CONCLUSION

The Cheatle-Henry extraperitoneal approach, through a Pfannenstiel type of incision, provides superior exposure for the liberation of the elements of the cords in cryptorchidism, without injury to the inguinal structures. Cases of unilateral and bilateral cryptorchidism were treated by this method with satisfactory results. Bilateral cryptorchidism can be managed through a single incision.

ADDENDUM

Since this paper was submitted for publication, 4 additional patients have been treated by this method.

J. S., 6 years old, underwent simultaneous correction of right undescended testis, right indirect inguinal hernia, and left indirect inguinal hernia.

B. T., 14 years old, underwent right orchidopexy. The procedure was modified by retraction of the rectus muscle medially.

H. A., 17 years old, had undergone right orchidopexy elsewhere which resulted in complete atrophy of the right testis. The left testis was intra-abdominal. Left orchidopexy was accomplished by preperitoneal dissection of the testis and cord components.

G. E., 8 years old, had bilateral cryptorchidism and hernias. Simultaneous orchidopexy and hernia repair were carried out.

A satisfactory result was obtained in each case.

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The blind-loop syndrome after gastric operations

THOMAS E. STARZL, M.D.*
GEORGE W. BUTZ, JR., M.D.
CHARLES F. HARTMAN, M.D.
CHICAGO, ILL.
From the Department of Surgery, Northwestern University Medical School

Since the earliest reports by White[68] and Faber,[19] it has been known that certain mechanical intestinal abnormalities could cause a hematologic syndrome which resembles pernicious anemia, and to date at least 100 examples have been reported. Location and etiology of the intestinal lesion varied, but the end result was stasis and retarded drainage from some portion of the gastrointestinal tract. Cases in which the stagnant loop was associated with certain specific absorption defects have been classified as examples of the blind-loop syndrome.[6, 14, 26] It is probable that only a small number of patients with anatomic blind loops develop the blind-loop syndrome with its metabolically important changes.

Two of the most common operations performed today in which potential stagnant loops are created are Billroth II gastrectomy and gastroenterostomy. The duodenum is converted into a side arm which rejoins the main intestinal tract at the gastrojejunostomy. It is common knowledge that this afferent loop occasionally drains improperly.[15, 30, 32, 37, 41, 42, 44, 46, 48, 53, 57, 58, 66, 67] However, prior to 1953, there were no well-documented reports of the blind-loop syndrome after either operation. Since that time, several examples of the blind-loop syndrome have been described after Billroth II resection or gastroenterostomy. The fact that only a handful of these cases has yet been reported may be due to the subtlety of the clinical manifestations, the difficulty of clearly establishing a diagnosis, and the general unawareness of this complication as a diagnostic possibility. In addition to its immediate clinical application, a consideration of the blind-loop syndrome may cast some light upon the nutritional superiority of the Billroth I over the Billroth II gastrectomy.

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*Markle Scholar.

ANATOMIC CONFIGURATION OF BLIND LOOPS

Various examples of gastrointestinal blind loops are shown in Fig. 1 for comparison with the blind loops observed after gastrectomy. These have occurred[6, 26] after creation of dead-end segments by anastomoses (Fig. 1, *A*), with jejunal diverticulosis (Fig. 1, *B*), with intestinal strictures which have most commonly been tuberculous in origin (Fig. 1, *C*), and after enteroenterostomies and fistulas (Fig. 1, *D*).

In experimental studies of the blind-loop syndrome by Tonnis and Brusis,[61] Pearse,[47] Watson and associates,[64] Taylor,[59] and Toon and Wangensteen,[60] a side-arm loop has been employed as in Fig. 1, *A*, in which the loop is arranged so as to be self-filling. The side loop arrangement is the one which most

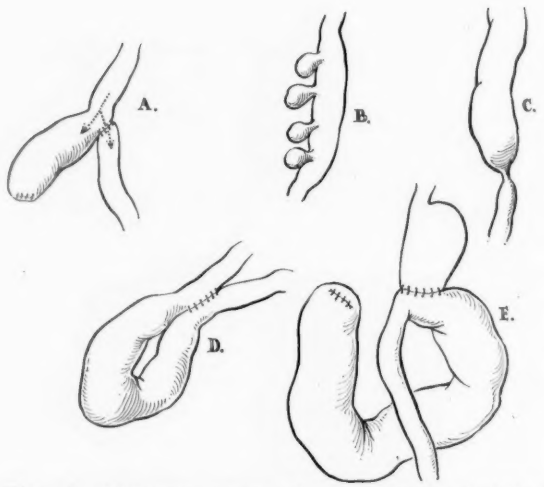

Fig. 1. Different types of gastrointestinal blind loops which have caused the blind-loop syndrome. *A,* Anastomosis with formation of a self-filled stagnant loop, *B,* with jejunal diverticulosis, *C,* with intestinal strictures, *D,* after enteroenterostomies or fistulas, and *E,* after gastric operation.

resembles a blind loop which develops after gastrojejunostomy (Fig. 1, *E*).

The structural conditions necessary for the blind-loop syndrome are not present after the Billroth I anastomosis. In all reported cases there has been either a Billroth II resection (8 patients) or a gastroenterostomy (1 patient). The anastomoses (Fig. 2, *A* and *B*) were both antiperistaltic, with the afferent loop to the greater curvature,[25, 45] and isoperistaltic.[13, 30, 45] In 2 cases (Fig. 2, *C* and *D*), an enterostomy had also been performed.[1, 49] Commonly, the afferent loop was excessively long and dilated.[25, 30, 45] The exact site of obstruction was sometimes difficult to define by roentgenogram or even at operation.[13, 45, 49] Usually, the distended loop ended abruptly at the gastrojejunostomy, but in some cases it extended beyond this. Excessively long afferent loops, kinking at the site of anastomosis, and partially obstructing adhesions have all been described as the factor causing blind-loop stasis.[1, 13, 25, 30, 45, 49]

ABNORMALITIES IN VITAMIN B_{12} METABOLISM IN BLOOD-LOOP SYNDROME

General information concerning the mechanism of the blind-loop syndrome has accumulated from observations on lesions at differing sites in the gastrointestinal tract. The principles involved apply, with variations, to blind loops at all levels. The best-known feature of the blind-loop syndrome is megaloblastic anemia, which is due to disruption of vitamin B_{12} absorption. Normally, dietary vitamin B_{12} (Castle's extrinsic factor) is absorbed after an incompletely understood interaction with intrinsic factor (Fig. 3, *A*), a mucoprotein secreted by the gastric mucosa.[22] In man, the principal site of B_{12} absorption is the ileum.[7, 8]

Vitamin B_{12} deficiency can develop by a number of alternative mechanisms. Rarely is there dietary deficiency of this nutritional factor. Commonly, as in pernicious anemia (Fig. 3, *B*) or after total gastrectomy,[39] there is absent intrinsic factor due to gastric atrophy or the absence of the stomach, respectively. Malabsorption can also occur[4, 23,

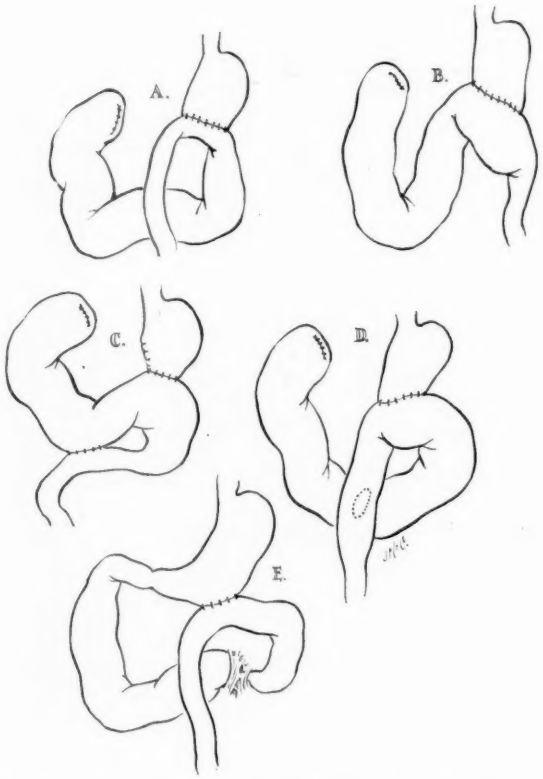

Fig. 2. Anatomic conditions after gastric operation which have caused blind-loop syndrome. *A,* 3 cases, *B,* 3 cases, *C,* 1 case, *D,* 1 case, and *E,* 1 case.

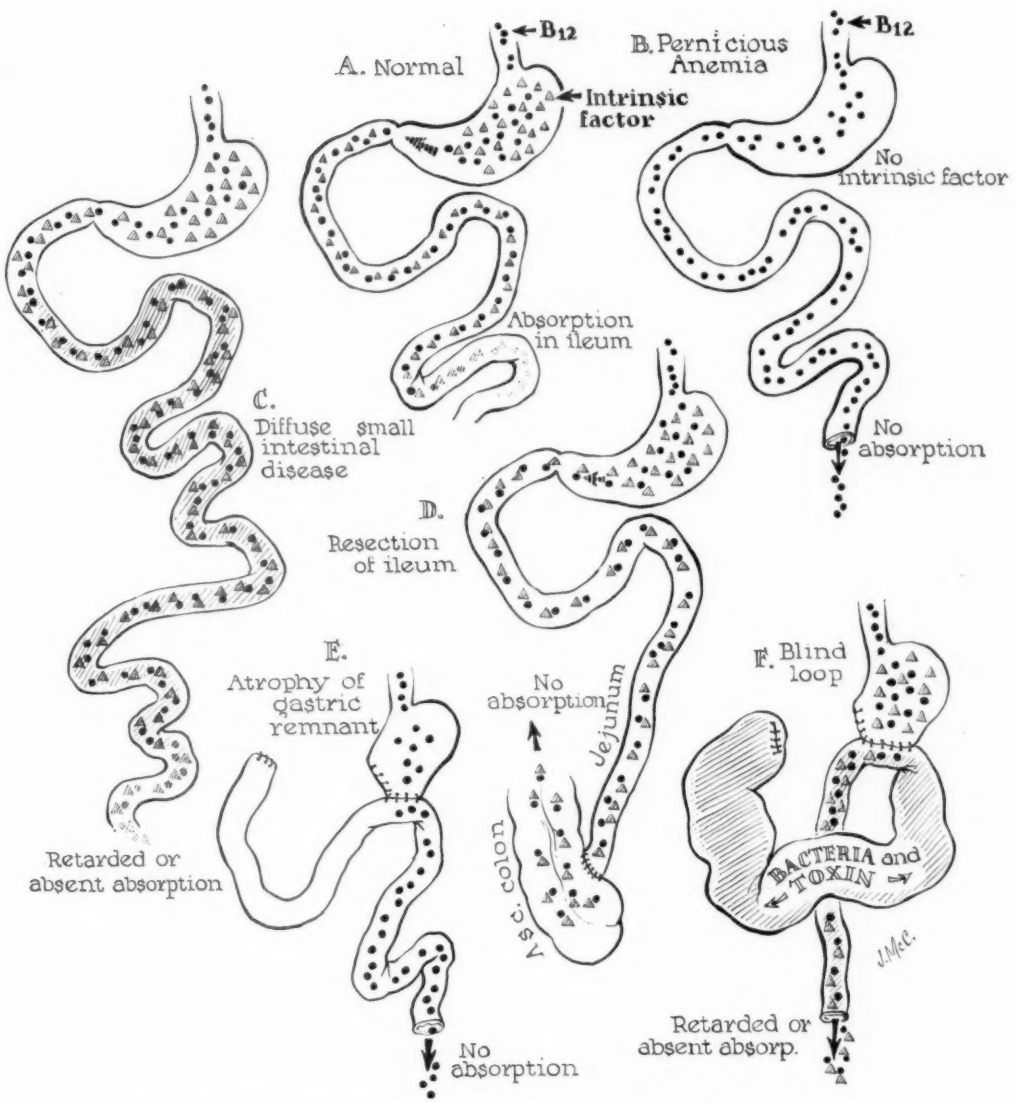

Fig. 3. Mechanisms of B_{12} utilization in normal and diseased patients.

[26, 27, 28, 35, 40, 43, 52, 54] with adequate intrinsic factor and dietary vitamin B_{12} in patients who have undergone ileal resection (Fig. 3, *D*) or who have diffuse small bowel disease (Fig. 3, *C*). Here, the malabsorption is due to damage or removal of the normal site of absorption. Vitamin B_{12} deficiency also develops in the blind-loop syndrome despite the presence of intrinsic factor and dietary B_{12} (Fig. 3, *F*). The malabsorption in this circumstance is thought to be due to bacterial overgrowth in a poorly emptying blind loop with consequent interference with B_{12} absorption in the remainder of the intestinal tract.[19, 25, 26, 50, 55, 56, 60, 65, 69] As with pernicious anemia, patients with blind-loop syndrome can proceed to subacute combined degeneration of the spinal cord.[1, 6, 26, 49]

Virtually all authorities agree that a change in the bacterial flora of the torpid loop is responsible for the B_{12} malabsorption. Much of the evidence is based upon clinical impression, but there is solid experimental work to support this opinion. Seyderhelm,[55] employing strictures to study the blind-loop effect in dogs, related the presence or absence of infection above the stenosis to the development or absence of anemia. Watson and Witts[65] have demonstrated in rats that the bacterial flora of small intestinal blind loops resembles that normally found in the colon. They also showed that the bacterial

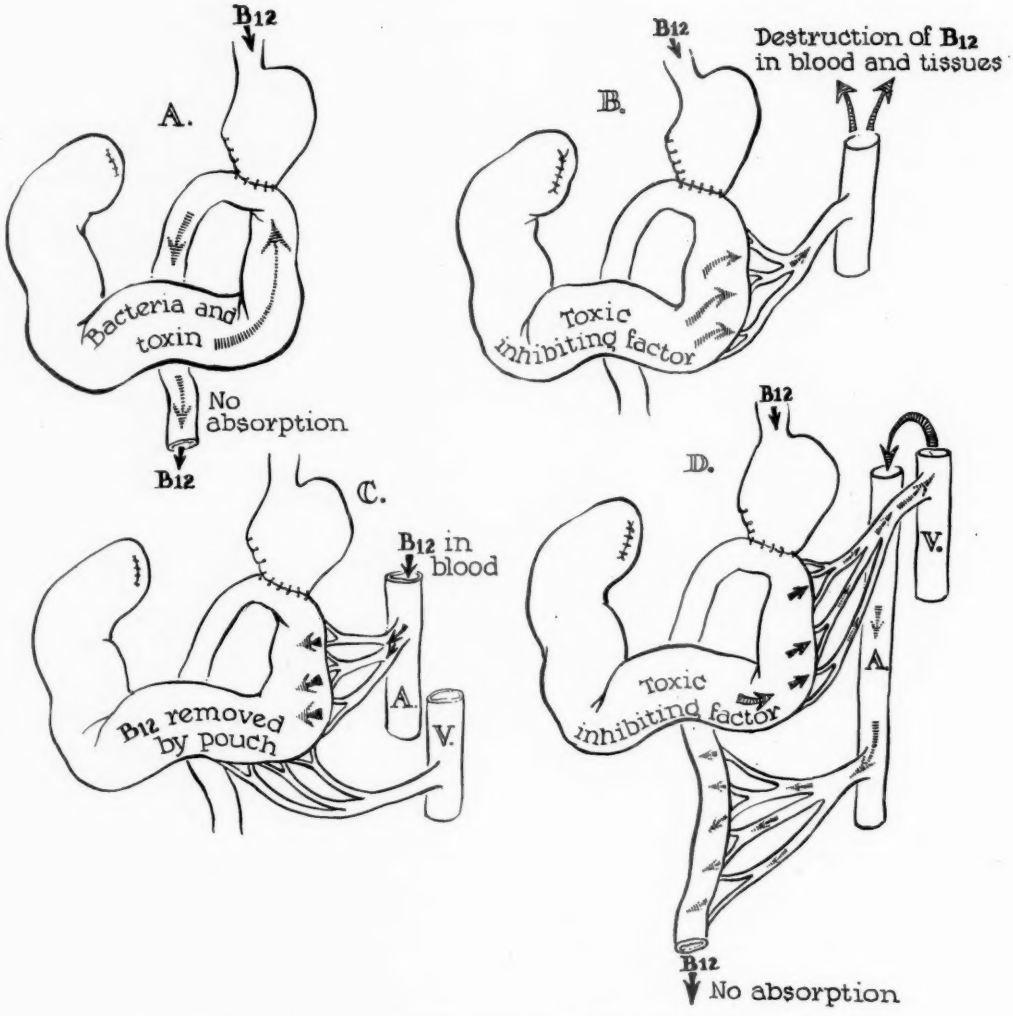

Fig. 4. Various hypotheses to explain malabsorption of vitamin B_{12}.

growth in the small bowel distal to the blind loop was changed with a reduction in Lactobacilli and increases in *Escherichia coli* and alpha hemolytic streptococci. Perhaps the most conclusive evidence for the bacterial etiology of the malabsorption was provided by Toon and Wangensteen,[60] and later confirmed by Watson and Witts.[65] These authors showed that the anemia of the experimental blind loop syndrome could be prevented by oral administration of chlortetracycline. The therapeutic value of antibiotics in man has been confirmed by Siruala and Kaipainen[56] and numerous other observers,[1, 3, 17, 25, 26, 28, 30, 34, 43, 45, 49, 50, 54] who noted that certain antibiotics could not only prevent the development of, but also reverse, B_{12} deficiency by restoring normal absorption of this vitamin. The application of these disclosures to the diagnosis and treatment of the blind-loop syndrome will be discussed subsequently.

Despite the generous support accorded the bacterial theory, the precise mechanism of vitamin B_{12} malabsorption is not known. One widely accepted theory is that propounded by Witts[69] in which B_{12} metabolism is supposedly affected by direct alimentary contamination of bacteria or their toxic by-products which spill out of the stagnant loop (Fig. 4, *A*). Since certain strains of *Escherichia coli* and *Streptococcus fecalis* metabolize folic acid or vitamin B_{12},[11, 51] it has been suggested that the anomalously located microorganisms use up the available oral supply. Contrary to this reasoning is the fact that Neomycin and sulphonamides, which

are nonabsorbable and which sterilize the nonstagnant intestine are of no therapeutic value[17, 25, 26] despite the fact that they would be expected to come into contact with efflux from the loop. In contrast, oral antibiotics such as chlortetracycline, oxytetracycline, and tetracycline can restore normal absorption of B_{12}.

However, if the offending agent were a toxin, its production in a sequestered loop would be suspended only with a systemic antibiotic. Drexler[18] has shown on the basis of in vitro experiments that indole compounds are able to inhibit normal utilization of vitamin B_{12}, and he has suggested that indole might be one of the blind-loop "toxins." Recently, Hoffman and Spiro[30] have failed to support either the bacterial or toxin theory of direct intestinal contamination. They instilled into a normal patient's stomach the contents of a resected blind loop with Co^{60}-tagged vitamin B_{12}. B_{12} absorption was not depressed.

Other theories to explain the B_{12} deficiency involve blood-stream mechanisms. Ungley[62] suggested that a toxin was absorbed from the blind loop which destroyed the vitamin in the blood and tissues (Fig. 4, *B*). He supported this opinion by the demonstration that plasma added from a resected blind loop suspended megaloblastic maturation in bone marrow culture. Card[16] also proposed that B_{12} was actually absorbed, but that increments were returned by enteric recirculation (Fig. 4, *C*) to the blind loop and destroyed. Both theories were weakened by the results of studies of urinary and fecal excretion of radioactive vitamin B_{12} which show that the block in metabolism is primarily at, rather than after, the absorption phase.[1, 3, 17, 25, 26, 28, 30, 34, 40, 43, 45, 49, 50, 54]

An unexplored possibility is that bacterial toxins are picked up from the blind loop and circulated to the uninvolved portion of the small bowel where they alter the absorptive capacity (Fig. 4, *D*). Such a hypothesis is compatible with the evidence obtained from antibiotic therapy, and with present knowledge of the fundamental defect in B_{12} utilization.

OTHER NUTRITIONAL DEFICIENCIES IN BLIND-LOOP SYNDROME

Absorption of other nutritional substances is often impaired. Fat is probably the most commonly affected. Using experimental mid-intestinal loops, Aitken and colleagues[2] found that virtually all rats exhibited steatorrhea whether or not the animals became anemic. The development of anemia alone, without steatorrhea, was uncommon.

As with vitamin B_{12} deficiency, it is thought that bacterial overgrowth in the blind loop is the causative factor in the steatorrhea. Specific evidence has been presented by Sammons[51] and by Goldstein and his group[25] that the bacterial growth adversely affects fat utilization. The latter authors have shown that the steatorrhea of the blind-loop syndrome is favorably influenced by antibiotics.

Why some blind loops do and others do not cause steatorrhea is not known. There is some evidence that the location of the blind loop is influential in this respect. Booth[7] has pointed out that a blind loop of the ileum, where normal vitamin B_{12} absorption occurs, may lead to pure B_{12} deficiency. Blind loops of the jejunum, where fat is normally absorbed,[7, 9, 25, 33] usually produce prominent steatorrhea.[4, 54, 63] While such localization is admittedly crude, it may help to explain differences in the malabsorption defect in different cases. Of 9 patients who had blind-loop syndromes after gastric operations, 7 had steatorrhea.

Other nutritional deficiencies are also common. Numerous cases of protein deficiency have been noted with blind loops at various levels, including the blind loops after gastric operations.[13, 25, 45] Usually this is reflected in low plasma protein levels, but 1 example of frank kwashiorkor has been reported in a patient with an intestinal blind loop.[36] Pellagra and vitamin C and vitamin K deficiencies have been recorded. Badenach[3] has warned against the dangerous complication of spontaneous retroperitoneal hemorrhage resulting from vitamin K deficiency.

INCIDENCE OF BLIND-LOOP SYNDROME AFTER GASTRIC OPERATIONS

The blind-loop syndrome has not been thoroughly evaluated as a cause of poor results after gastric operations. It is probable that this complication is more important than the 9 recorded cases[1, 13, 25, 30, 45, 49] indicate. For example, Kinsella[32] recently reported 7 cases which are probably examples of the blind-loop syndrome, but there is insufficient data to be certain of this. Several factors make the diagnosis an obscure and difficult one which is apt to be overlooked. First, the interval between operation and the onset of symptoms can be prolonged for many years, which tends to minimize the etiologic role of the remote operation in relation to the presenting complaints. In addition, the symptoms often are subtle and nonspecific and resemble psychoneurotic complaints.

Undoubtedly, an additional hindrance has been the preoccupation with macrocytic anemia as a prerequisite for this diagnosis. In point of fact, this feature may be absent as it was in 7 of the 9 cases collected in this review. Macrocytic anemia was frequently masked by prior vitamin B_{12} therapy or by the presence of other and equally important absorption defects of fat, iron, and other materials. Even in the untreated patient, the body stores of vitamin B_{12} are not dissipated for 3 to 4 years in the complete absence of B_{12} intake,[20, 21, 23, 28] so the development of megaloblastic anemia is a late manifestation. However, techniques and knowledge acquired in the past few years allow the blind-loop syndrome to be defined in terms of specific and measurable parameters of malabsorption rather than in terms of their end results. These techniques, outlined in the section on diagnosis, should increase the frequency and accuracy of detection.

It should be emphasized not only that macrocytic anemia is not a prerequisite to the diagnosis of the blind-loop syndrome, but also that most cases of megaloblastic anemia after gastric operations are not due to this cause. McLean[39] has summarized the results of investigations of patients with macrocytic anemia which developed after gastroenterostomy or partial gastrectomy. Almost invariably, these patients have developed atrophy of the gastric remnant with loss of the intrinsic factor (Fig. 3, *E*). Differentiating patients with the blind loop syndrome from those with gastric atrophy is a crucial step in correct diagnosis.

CLINICAL MANIFESTATIONS OF BLIND-LOOP SYNDROME AFTER GASTRIC OPERATIONS

The clinical features of the blind-loop syndrome are seldom overt. The diagnosis has usually been made only after months or years of disability. Commonly, a gastroenterostomy or Billroth II gastric resection performed as long as 26 years previously had initially been considered to have a good result. When anemia, weight loss, malaise, hypoproteinemia, steatorrhea, or neurologic complaints developed, the possible relation to the previous operation was often overlooked.

Anemia was present in all cases.[1, 13, 25, 30, 45, 49] In only 2, however, was it macrocytic in type.[1, 45] Steatorrhea was the next most common feature and was found in 7 patients.[1, 13, 25, 45] Five of these had diarrhea. Some evidence of malnutrition was always present, and 5 patients had edema or hypoproteinemia.[13, 25, 45] Glossitis, blepharitis, cheilosis, or other signs of vitamin deficiency were seen in 3 patients. Neurologic findings suggestive of subacute combined degeneration of the cord were present in 3 patients with calf pain, changes in deep tendon reflexes, and decreased sense of vibration and proprioception.[1, 13, 49]

Vomiting and abdominal pain were reported in 1[30] and 3[1, 13, 30] cases, respectively. The vomitus consisted of pure bile or foul brown material, and the emesis probably resulted from convulsive emptying of the blind loop. Sporadic bilious vomiting is known to be a characteristic symptom in patients with an obstructed or distended afferent loop,[15, 30, 32, 37, 41, 42, 44, 46, 48, 53, 57, 58, 66, 67]

and it is possible that this symptom will prove to be common as more information accumulates concerning the blind-loop syndrome.

DIAGNOSIS

Radiologic studies may be helpful in establishing the presence of dilatation or stasis in the afferent loop. In some cases, barium entered a dilated, tortuous loop.[25, 30, 45] In others, barium was held up, often for many hours, in an unidentifiable pouch (Fig. 5) near the gastroenterostomy.[13, 49] In some, barium did not enter the afferent loop.[49] In a recent study of afferent loop obstruction, Kinsella and Hennessy[32] reported the various radiologic features of afferent loop obstruction to be (1) absence of barium passage into afferent loop, (2) passage of barium for 1 to 2 cm. into the afferent loop with an abrupt halt at an obstruction, and (3) pendulum effect with passage into the afferent loop and remittent emptying back into the stomach.

During the last 10 years, laboratory techniques have been developed which allow the diagnosis of the blind-loop syndrome to be made with increasing precision. First among these are tests employing Co^{60}-tagged vitamin B_{12} either for determination of fecal excretion,[29] hepatic uptake,[24] or urinary excretion.[52] The urinary excretion method, the Schilling test,[52] is the most widely used. The patient is given 0.5 to 1.0 μg of Co^{60}-tagged B_{12} orally, and 2 hours later a flushing dose of 1,000 μg of nontagged B_{12} is given intramuscularly or subcutaneously. The amount of radioactivity in the ensuing 24-hour urine specimen provides an indirect measure of the amount of oral Co^{60}-tagged B_{12} absorbed. Normally 8 to 40 per cent of the Co^{60}-tagged B_{12} is excreted in the urine.

When urinary excretion of the Co^{60}-tagged B_{12} is subnormal or absent, the test is repeated with concomitant oral administration of intrinsic factor. In cases of pernicious anemia and in postoperative patients in whom gastric atrophy has occurred, urinary excretion will be restored to normal, and the diagnosis of blind-loop syndrome is excluded.[5, 10, 23, 38, 39]

If the combination of Co^{60}-tagged B_{12} and intrinsic factor does not increase urinary excretion, the blind-loop syndrome becomes a strong possibility. Co^{60}-tagged B_{12} is again given, this time after several days of therapy with tetracycline, chlortetracycline, or oxytetracycline. In many cases, the antibiotics restore absorption and the urinary excretion will become normal. Should this occur, the diagnosis of blind-loop syndrome is virtually established.[1, 3, 17, 25, 26, 28, 30, 34, 43, 45, 49, 50, 54] Failure of the antibiotics may be due to Whipple's disease, sprue, or some other diffuse intestinal disease, or to surgical absence of the ileum. It does not preclude the possibility of the blind-loop syndrome, however, since the bacteria of the blind loop may not be sensitive to the antibiotics used.[13, 17, 25, 43]

Fig. 5. Gastrointestinal series in patient with blind loop syndrome after Billroth II gastrectomy. Note pouch at gastrojejunostomy site and dilated and elongated afferent loop (left). Barium remained in pouch for 6 hours.

Experimental and clinical data previously alluded to emphasize the importance of studying the absorption of other substances, particularly fat. Jackson and Linder[31] and Butler and associates[12] recognized the resemblance of gastroenterostomy and Billroth II gastrectomy to the better-known intestinal blind loops. They speculated that bacterial growth in the afferent limb might account for the higher incidence of steatorrhea after Billroth II than after Billroth I gastrectomy. Recently, Goldstein and his colleagues[25] studied bacterial counts by afferent limb intubation in postoperative patients, and demonstrated a strong correlation between the degree of contamination in the afferent loop and the magnitude of steatorrhea. They also showed that antibiotic therapy reduced steatorrhea, presumably by the same mechanism as B_{12} absorption is improved in other blind loops. This type of testing may prove to be of great value in the study of postgastrectomy malabsorption syndromes and in the detection of afferent blind loops.

Other tests may be useful in individual cases. Gastric analysis for acid should always be carried out, since the presence of free acid excludes gastric atrophy as a cause of B_{12} malabsorption. Badenach[5] has performed endoscopic gastric biopsy and studied urinary uropepsinogen in order to evaluate the secretory capacity of the stomach.

In the diagnosis of the blind-loop syndrome, reliance upon a single symptom, finding, or abnormality of absorption is not wise. The absorption defects are frequently multiple, and other deficiencies may be of greater importance than those which would lead to a specific hematologic picture. Unification of the different aspects presented by the blind-loop syndrome into a well-understood entity would undoubtedly lead to a higher rate of recognition of this complication of gastric operations.

TREATMENT OF THE BLIND-LOOP SYNDROME AFTER GASTRIC OPERATION

Medical therapy can temporarily improve the health of patients with the blind-loop syndrome. With tetracycline, chlortetracycline, oxytetracycline, chloramphenicol, and possibly other antibiotics, the absorption of vitamin B_{12}, fat, and probably other nutrients may be restored toward normal. The improvement may outlast a course of antibiotic therapy by weeks or months,[1, 25, 54] but relapse eventually is expected. Specific vitamin deficiencies, especially of B_{12}, should be corrected. High protein, high calorie diet, correction of low blood volume, and restoration of electrolytes are other adjuncts.

Definitive therapy requires surgical correction of the blind afferent loop. In the 9 collected cases, 6 patients had been operated upon at the time of the report.[13, 25, 30, 45, 49] In 4, the Billroth II anastomosis was taken down and converted to a Billroth I,[13, 25, 45, 49] and in a fifth similar reconstruction was carried out with the interposition of a jejunal segment between the stomach and duodenum.[45] A good result was obtained in all with complete or partial correction of the pre-existing absorption defects. In the sixth case, the dilated and elongated afferent loop was resected and a short-loop Billroth II anastomosis performed with a good result.[30] From a mechanical point of view, other operations have been proposed for the treatment of afferent loop obstruction, such as enteroenterostomy, jejunoplasty, support of the afferent loop by suture, and defunctionalization of the afferent loop by Roux Y anastomosis. There are objections to each of these operations, especially in terms of late results, and they probably should not be used.

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Pancreaticojejunostomy for chronic relapsing pancreatitis: an evaluation

WILLIAM J. GILLESBY, M.D.
CHARLES B. PUESTOW, M.D.
HINES, ILL.
From the Hines Veterans Administration Hospital

It is generally agreed that ductal obstruction is a major etiological factor in the production of pain and the development of chronic relapsing pancreatitis. The literature has been and continues to be plentiful with regard to methods of accomplishing adequate drainage of the pancreas.

The concept[7, 12] that adequate decompression and drainage of the pancreas would relieve the symptoms of chronic relapsing pancreatitis has been supported by the results. Carnevali and associates[3] have experimentally supported the belief that "unroofing" of the pancreatic ducts and anastomosis of the surrounding pancreas to the jejunum is a practical and physiologic procedure.

Bartlett and Nardi[2] have utilized some of these principles with success. They mobilized the pancreas and opened the ducts widely, then performed a vagotomy and gastric division with implantation of the opened pancreas into the isolated antrum of the stomach. Their belief was that by adequate drainage as well as suppression of pancreatic secretion accomplished by means of the vagotomy, they would relieve the symptoms of pancreatitis. They have reported success in a limited number of cases. From our own studies we suspect that the intragastric pancreas is slowly digested and that one of the aims of this treatment, namely, preservation of pancreatic tissue, is thus defeated.[10]

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Partington and Rochelle[8] have modified the procedure in an interesting way. They leave the pancreas in situ without removing the spleen and anastomose the opened pancreas to the opened jejunum. In recent cases and as recently reported,[4] we have been performing a somewhat similar procedure by anastomosing the opened pancreas to the opened defunctionalized jejunum, but have not been as successful as Partington and Rochelle in preserving the spleen.

The preservation of the spleen is desirable, but the adhesions between spleen and pancreas in these cases are frequently quite dense and minimal manipulation tears the splenic capsule and makes splenectomy mandatory. The splenic vessels are adherent to the pancreas and must sometimes be ligated to allow mobilization of the spleen. Partington and Rochelle have suggested that splenorenal shunt is to be considered in some of these cases because of the accompanying portal hypertension. We have found that splenorenal shunts in these instances are technically difficult if not impossible, because of the peripancreatic reaction. Preston[11] has treated 2 patients with traumatic splenic rupture in association with chronic relapsing pancreatitis. He believes the rupture occurred because of fixation due to inflammatory reaction and minor trauma to the left side. We have treated 2 such patients and have seen 3 at operation when minimal manipulation of the pancreatic tail resulted

in tears in the capsule and hilar pulp which necessitated splenectomy.

Of personal communications[1, 3, 4, 6, 8, 9, 13, 14] with surgeons who have performed retrograde pancreaticojejunostomy (some 25 cases) in the manner we have described, only 2 poor results have been reported.

Twenty-nine patients have been treated by the "opened pancreas" pancreaticojejunostomy method. There was 1 postoperative death. The patient died 30 days postoperatively of peritonitis which was deemed at postmortem examination to be due to a leak in anastomosis. This, we believe, was due to a technical error and could have been avoided by paying more attention to some of the details learned later. Our analysis of these cases places 19 results as excellent, 4 as good, and 2 as fair to poor.Two patients were lost to follow-up. There was one other death. One patient who was lost to follow-up had experienced dramatic relief of pain and had been in excellent condition when last seen 7 months postoperatively. Chronic relapsing pancreatitis had occurred in a paraplegic patient and he was operated on at this institution. Pain was relieved promptly and he was quite well except for numerous urinary tract problems which so often occur in the paraplegic patient. He died 1 year after operation of cirrhosis, chronic brain syndrome, and hemorrhagic cystitis. No postmortem examination was obtained, but the relief of pain had been complete. Two patients showed poor results and no explanation is known. In both of these cases the pancreatic ducts were almost obliterated and the fibrosis and scarring of the pancreas made us wonder if drainage could be accomplished by any procedure. The 4 patients with good results have been well, but occasionally have short bouts of pain which we suspect accompanies alcoholic excess. Of the 19 patients with excellent results, the pain has been relieved in a dramatic fashion. A short description of one of these, an alcoholic individual with chronic relapsing pancreatitis, may be of interest. He had a history of numerous surgical procedures in various institutions. In 1952 he had undergone a gastric resection, later a splanchnicectomy, and later a celiac ganglionectomy. In 1954 a sphincterotomy had been performed without relief. Cholecystectomy was performed 6 months later. In 1956, when he was first seen at this institution, a retrograde pancreaticojejunostomy was performed by our original method,[12] with implantation of the pancreatic tail into a Roux Y jejunal loop and restoration of the intestinal channel performed by a Roux Y anastomosis. The man was relieved of pain and had been well for approximately 9 months when pain recurred. At this time it was decided that a more adequate drainage procedure should be performed and in 1957 reoperation was carried out. The pancreas was opened widely and drained into the defunctionalized jejunal segment. Recovery was uneventful and the man has been well. He has some dumping syndrome symptoms, his weight has increased, and the steatorrhea has markedly improved. Calcifications which

Fig. 1. Cholecystogram which shows normally functioning gall bladder with marked calcification throughout the pancreas. These calcifications are not confined to the pancreatic ductal system.

were present in the pancreas over the years have disappeared on roentgenogram.

Most of the patients have been of the alcoholic type and few of those treated have ceased drinking. In reviewing the charts, we noted in most of them the comment that the patient smelled strongly of alcohol. Two operations have been performed when chronic relapsing pancreatitis followed gastric procedures with damage to the pancreatic ducts. One of these operations followed a gastric resection performed elsewhere which had been complicated by postoperative pancreatitis. The patient had a long history of pain and debility which had brought him to the point of psychosis. After observation it was decided to attempt to do something for this unfortunate individual and a reconstruction was carried out. Retrograde pancreaticojejunostomy with Roux Y reconstruction was used. The pain was dramatically relieved, his disposition improved, and he was discharged from the psychiatric section of this institution. Follow-up 6 months postoperatively showed that he was well and believed that he could go back to work soon.

The question has long been in our minds as to whether or not the pancreatic ducts remain open. We have some evidence that they do. A 37-year-old Negro man was first seen in 1956 with intractable pain. He was requiring large doses of narcotics. Medical management failed. Cholecystectomy and common duct exploration were performed with a sphincterotomy. He was not improved and in 1958, a retrograde pancreaticojejunostomy with a Roux Y enteroanastomosis was performed. The patient did well, but had recurrence of pain and in March, 1959, the pancreaticojejunostomy was revised. The dilated duct was opened widely on this occasion and the man recovered well after this procedure. Some 7 months later, he died of an acute myocardial infarction and at postmortem examination the pancreas was markedly constricted and fibrotic, but draining into the jejunal pouch. The postmortem report stated that the pancreaticojejunostomy was

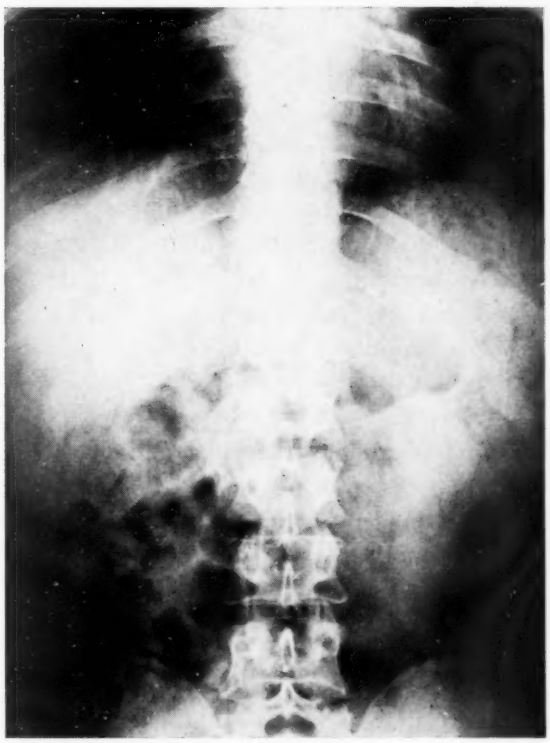

Fig. 2. Cholecystogram taken 1 hour after ingestion of a fat meal. There is satisfactory gallbladder emptying.

Fig. 3. Upright film of abdomen taken 4 years later. Calcifications have disappeared.

functioning well, and we know from the patient's history that the pain had been completely relieved.

Microscopic sections taken preoperatively and 7 months later showed fibrosis and scarring. The preoperative sections showed more leukocytic reaction than the postoperative sections, but we have not as yet found evidence of dramatic glandular regeneration. In view of the studies of Carnevali and associates in dogs, we believe that glandular regeneration may occur.

The pancreatic calcification may be dissolved after pancreaticojejunostomy. Figs. 1 and 2 show calcification throughout the pancreas in a 32-year-old salesman who had a past history of alcoholism. He has been relieved of symptoms after adequate pancreatic drainage by pancreaticojejunostomy. Fig. 3 shows disappearance of the calcifications 4 years later.

SUMMARY

An analysis of adequate drainage of the pancreas has been presented. We are convinced that pancreatic pain is due to increased pressure within the gland secondary to ductal obstruction and, on clinical grounds, that some recovery of the pancreas occurs after adequate drainage. In these cases the condition has been severe and the alcoholic patients have not been reformed by their disease.

Simplification of the procedure is continuing and we believe that as more surgeons attempt it, new ideas will be developed and the procedure will become standardized. It is our firm belief that the pancreatic duct should be widely opened and adequate drainage provided. No attempt should be made to make a mucosa-to-mucosa anastomosis between the pancreatic duct and the jejunum. The jejunum should be anastomosed to the outer surface of the pancreas some distance from the edges of the pancreatic incision. If this is performed, the results so far are gratifying and well worthwhile.

ADDENDUM

Three additional surgeons have reported good results in individual cases since preparation of this manuscript.

We would appreciate hearing from surgeons who have performed this procedure.

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